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CONSTITUTIONAL VARIATION AND SUSCEPTIBILITY TO DISEASE *

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The conception of disease as a product of a constitution is a heritage from antiquity, based on observation and experience.[1] As is well known, the term constitution was originally used in a broad sense to denote a fixed or a prevailing state or condition. It was applied primarily to climatic and meteorological conditions, but was also used with reference to disease and to man.

To the ancient Greek, disease was a product of the interaction between man and his environment; still, environment was given first place, much as it is today, but for a different reason. The Greek regarded both man and disease as products of environment, while in recent years investigators have been inclined to disregard man and to stress the importance of a single environmental factor. This change of views is attributable to modern bacteriology. After centuries of abstract speculation concerning the cause of disease, bacteriology came like a beam of light into the darkness; micro-organisms were realities and offered the first hope of the solution of the problems of disease by the use of scientific methods. Bacteriology and immunology were like new toys. For the time being, man and his environment were cast aside and attention was focused on the so-called causative agents of disease and on the reactions produced by them when introduced into the body. New conceptions of disease were evolved with man and the micro-organism as the central figures. Subconsciously, the old idea of disease as a product of the interaction between man and his environment was first supplanted by the idea of an interaction between man and an infecting organism. Eventually, this simplification was carried

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1. The ancient conception of the relation between man and his environment is clearly set forth in the hippocratic treatise on "Airs, Waters, and Places" which is one of the most remarkable medical documents of all times. It contains many of the fundamental ideas of the modern conception of human constitution and climatology, including the factors of heredity and the beneficial effects of sunshine. It is also remarkable for the accuracy of the observations made when viewed in the light of results of present day experiments. In this connection, it will be noted that the results of many of the experiments referred to in this paper are neither more nor less than confirmations of hippocratic teachings translated into modern terminology.

still further. The causative agent of disease became the important factor, while man was assigned the rôle of the victim, or object, rather than the subject of disease. In this new form, the idea of interaction between host and infecting organisms was verbally retained, but it was given scant consideration in explaining phenomena of disease, except when some specific reaction was concerned. In processes of reasoning, the micro-organism became endowed with many potentialities, both real and imaginary, while the host came to be regarded in somewhat the same light as a standard culture medium. Any deviation from the usual or expected course of events was attributed to some change affecting the micro-organism; it rarely occurred to any one that the condition presented might be attributable to the host, and even if it did, there was no means of explaining the observed facts. So it came to be considered that a man was just a man and an animal just an animal, fixed and immutable, but a micro-organism was a being endowed with infinite potentialites.

A paradoxical situation was thus created. The importance of such factors as age, sex, family, race and even individual predisposition was clearly recognized; so were the factors of climate, season and weather, but these factors were still abstract conceptions and could not be fitted into a scheme of things founded on the results of carefully controlled experiments which dealt with micro-organisms and defensive or immunologic reactions. It was inevitable, therefore, that explanations of phenomena of disease should depend more and more on the body of accumulated facts concerning micro-organisms and that less consideration should be given to factors which were not understood or which represented vague and intangible quantities.

Apparently, the pendulum has completed its swing in this direction. There is a reawakening of interest in the host and his environment, with a growing realization of the fact that in infectious diseases there are two systems of variables, and that one cannot hope for a satisfactory solution of the problems so long as one arbitrarily treats either system as a constant and attributes all variations in results to the other. The problem which now confronts one is to define the potentialities of both systems in terms that can be clearly understood. Until this has been done, the analysis of phenomena of infection and disease will be attended with considerable uncertainty.

The study of constitution is only one phase of this great problem, but during recent years much has been done to clarify the relation of man to disease. This is particularly true of the work that has been done in genetics, endocrinology, dietetics, biophysics and the field of epidemiology itself. Finally, under the leadership of Draper, a notable effort has been made to adapt the precise methods of anthropology to medical requirements and to apply these methods to clinical medicine.

Still, it is extremely difficult to define the constitutional factor in language which conveys a definite meaning or to say how or why one person differs from another, with respect to the general property of susceptibility to disease, or why this property should appear to vary from time to time in a given individual or in a population as a whole. Simple observation and experience tell one that these things are true. No medical tradition is more firmly rooted in the minds of all peoples than this. Moreover, these conditions are applicable to animals as well as to man; one sees them continually in experimental work. They cannot be denied or ignored. They must be explained as simply and directly as possible, and I have taken this for my task, with a full realization of the fact that any explanation that may be offered at this time must be incomplete and is subject to amplification, modification or complete abandonment, as future developments may demand.

THE PROBLEM OF CONSTITUTION

There are two firmly established aspects of the problem of constitution, namely, heredity and environment. From the point of view of the bearing of constitution on susceptibility to disease one has to consider the question of factorial potentialities on the one hand, and the functional expression of these potentialities on the other. For the most part, interest in constitution has been centered in problems of heredity and in the study of normal and abnormal constitutional types. For obvious reasons, less attention has been paid to conditions presented by the rank and file of mankind, but it is this phase of the subject in which I am especially interested, as it seems to me that a knowledge of the fundamental principles of constitutional organization and reaction is a prerequisite to the study of any class of persons or of the relation of man to disease. So far, I have been concerned primarily with the study of existing states—physical, chemical and functional—and with the influence exerted by environment on the constitutional status and its functional expression as determined by variations in the reaction to disease.

The conception of the relation between constitution and susceptibility to be presented is merely an outline of certain phases of a complex problem. It is based on experiments which have been in progress for about ten years, and represents the combined efforts of Dr. L. Pearce, Dr. C. M. Van Allen, Miss Marion Howard, Dr. A. R. Harnes, Dr. A. E. Casey and me. A great deal of the material to be used has been published, but unfortunately much of it is still in the process of digestion and assimilation. I shall, however, confine myself to facts which have been amply demonstrated.

The problem of constitution turns, first of all, on the determination of what is normal. The usual treatment of this subject is unsatisfactory.

The current method of dealing with normality is the method of standardization—the establishment of mean values with limits of variation or of other standards of measurement and the separation of persons into two classes, the normal and the abnormal. It is apparently assumed either that what happens within the limits of normal is of no consequence or that the methods available for drawing distinctions are inadequate. The territory marked off by the upper and lower limits of normal has been entered with the intention of finding out whether normal is just normal or whether something more can be said. A common laboratory animal, the rabbit, has been used, which could be taken apart and, theoretically, reassembled at will, and could be used in an attempt to correlate states of normality with susceptibility to disease, or in studies of the influence of heredity, as well as for collateral studies of constitutional effects produced by disease and effects of constitutional modification on disease itself, whether produced by mechanical, chemical or physical means. In general, this is the field which our studies have covered.

As an approach to the discussion of the problem, one may consider the animal organism to be divisible into three parts: (1) a skeletal and muscular system which is concerned primarily with the performance of mechanical functions or with doing the physical work of the body; (2) a system of organs which carry on and regulate vital processes and support the muscular and skeletal systems, as it were, and (3) the blood and lymph which form a medium of communication and exchange between all parts of the body and, in addition, have particular functions of their own to perform. For present purposes, however, it is not necessary to consider the function of any organ.

It is a well recognized fact that all animals of a given species are constructed in accordance with a common plan and with some regard to quantitative relations between the various parts of the body. Normal functional activity is dependent on the maintenance of these relations within certain prescribed limits, but the limits are sufficiently wide to permit of variation, which is the basis of individuality.

While everyone is aware of the fact that persons differ from one another in respect to the size or weights of organs or parts of the body, just as they do in appearance or other physical characters, there are probably few who have attempted to reduce the question of organic individuality to the basis of a measurable difference. I shall begin, therefore, by assembling organs for three hypothetic animals, using maximum, minimum and mean values per unit of body weight for representative organs as determined by actual observations on a group of 645 normal rabbits. When presented graphically (chart 1) the difference is striking.

Of course, no such animals as these exist nor is it likely that persons of the extreme types could exist. Still, there are animals which differ in one or more of these respects by amounts equal to those

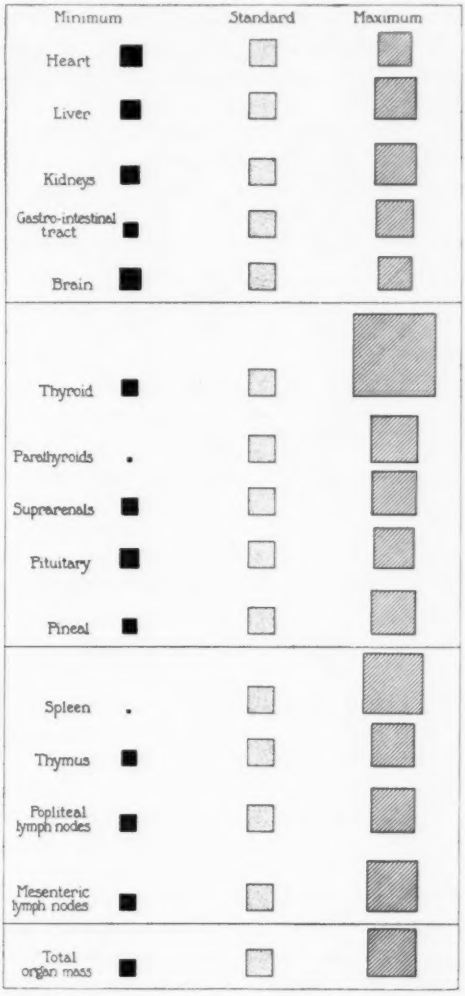

Chart 1.—Theoretical range of variation in organic constitution of normal animals. Weights per unit of body weight.

indicated in this diagram. A four or five-fold difference in the weight of an endocrine gland or of a lymphoid organ or a twofold difference in the weights of parenchymatous organs, per unit of body weight, is

by no means uncommon, while variations of from 25 to 100 per cent are common. The smaller variations are of the order of the differences in weight or in stature of adult men but in some instances the extremes exceed the difference between dwarf and giant.

These differences in organic constitution are not hypothetic but real, and they raise a second point of fundamental importance, namely, the relation between the weight of an organ, or an assemblage of organs, and the weight of the body which they serve. Within certain limits, the actual weight of most organs and, therefore, the combined mass of all organs, varies directly with the weight of the body, but the exact relations are such as to produce a decided difference in the constitution of large and small animals. There is a tradition to the effect that, in general, large, robust persons are frequently more sus-

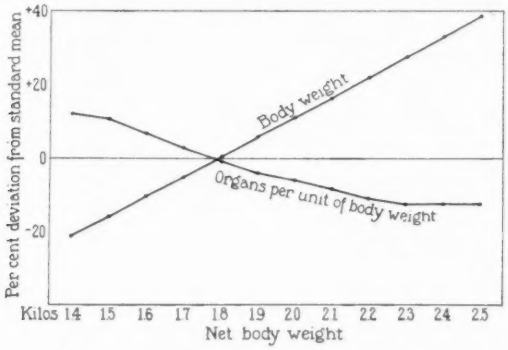

Chart 2.—Organ-body weight relation for animals of different weight groups.

ceptible to disease than those of the small, wiry type, and that in illness the prognosis is less favorable. This may or may not be true, but there is a constitutional parallel which might warrant such an expectation. The fact is that the mass of organs in proportion to the weight of the body served is distinctly greater for small than for large persons (chart 2). By weighing the results for all organs so as to give them equal value irrespective of size, it is found that, despite the fact that the actual weight of organs increases with the weight of the body, the weight per unit of body weight actually diminishes. Hence, the normal load carried by the organs of small persons may be less and the reserve greater. Applied to the maximum and minimum animals, this means that the constitution of the smaller person approaches the maximum type, while that of the larger assumes the direction of the minimum type. From our material, it cannot be determined with certainty whether this relation is due primarily to breed, age or weight,

independent of these factors, as the condition appears to be one which is influenced by all the factors mentioned.

At any rate, it will be seen that the relation of organ mass to body weight, individually and collectively, is one of the basic principles of organic constitution and is applicable to breeds or races, families, sexes, age groups and individuals.

As is well known, physical characters such as weight and height are distributed in accordance with the laws of normal or chance distribution. The same is true for the weights of organs and, hence, for organic constitution; that is, in an animal population there is a constant and approximately equal number of animals whose organ mass, in proportion to body weight, is above or below the mean or mode, but in reality most of the curves are skewed or tend to be extended somewhat into the upper ranges, as is the case with measurements of height and body weight. As a simple working formula, it may be said, however, that small, intermediate and large organs will be encountered in the ratio of 1:3:1. The significance of these proportions will appear later.

Individual differences of organic constitution may be regarded as inherent qualities in that they are probably determinied in accordance with the principles of genetic inheritance. They represent potentialities, however, rather than fixed qualities. So far as I have been able to determine, no organic relation or status is absolutely fixed. It is well known that organs change with age and that some, at least, show periodic variations of a seasonal character or in association with some change in physiologic status, such as pregnancy. There is, however, no clearly defined idea of what these variations represent from the point of view of their collective effect on constitution, broadly considered. This situation has, to some extent, been clarified.

I have data on the variations in weight of seventeen representative organs covering a period of three and one-half years. If the results for the entire period are condensed to the basis of a single year, one may obtain an idea of the extent to which different organs vary per unit of body weight and the trend of the variation from month to month (charts 3, 4 and 5). In the first place, one finds that, strictly speaking, not one of the organs studied maintained a constant relation with the body. Even the heart, the kidneys and the brain showed slight but definite variations; of course, the endocrine and lymphoid organs showed the greatest variations.

Without attempting a detailed analysis of the trends of curves, it will be seen that, in a general way, they partake of a seasonal character with distinct differences in the time and direction of the variations. In some instances, there were four clearly defined fluctuations during the year. The thyroid presents a curve of this type with an increase in winter and early spring, a decrease in late spring and early summer,

an increase in midsummer which, in the present instance was even greater than that in winter and a marked decrease in the autumn. The curves for the parathyroid, pituitary and pineal glands are of a simple diphasic type with maximum values in midsummer and minimum values in the winter. While I am not now concerned with interrelations, I may

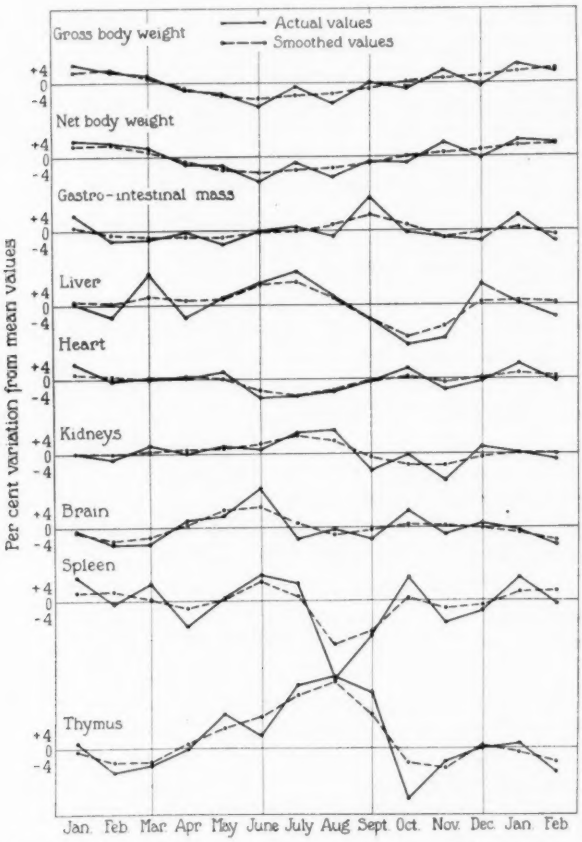

Chart 3.—Variations of body and of organ weights per unit of body weight.

call attention to the fact that in some instances the relation between organs is direct and in others inverse, or that for one period of the year the relation may be direct while for another it is inverse.

The variations shown may appear to be too complicated to permit of interpretation, but certain features of their meaning can be made clear by the use of a simple system of grouping and combination of

results. For this purpose, the organs may be divided into three groups: the first group including the heart, liver, kidneys and brain; the second, the endocrine glands and the third, the lymphoid organs.[2] I shall assume that the organs of the body are provided in such numbers and

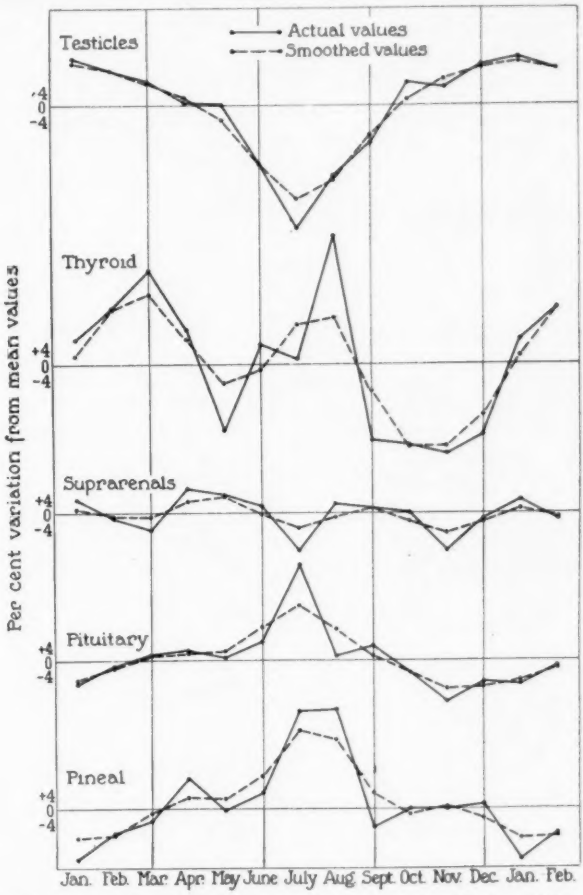

Chart 4.—Variations of organ weights per unit of body weight.

sizes as are necessary for the performance of their functions. If this is true, the organs should be dealt with so as to be given an equal value

2. The thymus is grouped with the lymphoid organs on account of its relation to the spleen, but without prejudice as to its relation to other organs. The gastro-intestinal tract and testes are omitted, but their inclusion would not alter the results as given.

irrespective of size. In the present instance this can be done by combining the results for the organs of each group on the basis of the algebraic sum of the percentage deviations from mean normal values (chart 6). In this way, a single curve is obtained for each group of organs, but in these curves each organ has the same value, just as one assumes that it has in the body.

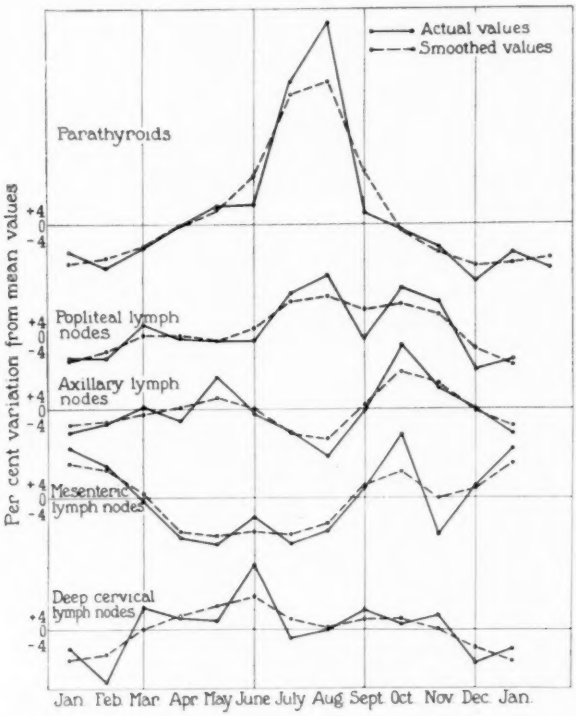

Chart 5.—Variations of organ weights per unit of body weight.

These curves enable one to visualize variations in terms of systems which differ somewhat in the character of their functional activities. Carrying this idea a step further, the three system curves may be combined, and thus a single expression is obtained of the relation that exists from month to month between the body as a whole and the total mass of organ tissue on which it depends for the maintenance of its various activities. This relation may be spoken of as the organ balance, and is expressed as a positive or a negative percentage deviation from a standard or a mean normal value. It is represented here as an

aggregate value, but in other places, it has been found more convenient to deal with it as a mean which, of course, does not alter the relation as here presented.

The reduction of the organ-body weight relation to a simple expression of a positive or a negative balance places this feature of the seasonal variation in constitution on a basis that is easy to comprehend.

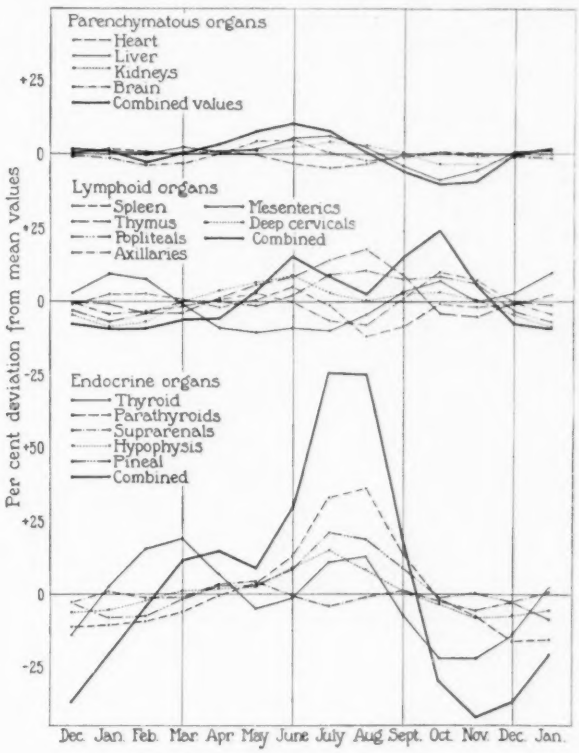

Chart 6.—Integration of organ systems.

If organic constitution has any functional significance, it is not difficult to imagine that with the changes in organ balance which occur from month to month there must be some changes in functional potentialities and that such changes might well include variations in susceptibility to disease.

The increasing balance during the first half of the year, with an interruption of the progressive movement in the spring, and the decreasing balance during the second half of the year, with high values in

summer and low values in fall, are significant features of the seasonal variation. It will be noted that the changes in organ balance virtually parallel the curves for sunshine, or solar radiation, temperature, absolute humidity and other meteorological conditions (chart 8). However, while some organs tend to follow the direction of the seasonal trend, others show an interesting relation to the deviation of meteorological conditions from the normal (chart 9). In the present instance, the lymphoid system showed a direct relation with the deviations of the sunshine curve from September to March and an inverse relation from March to September.

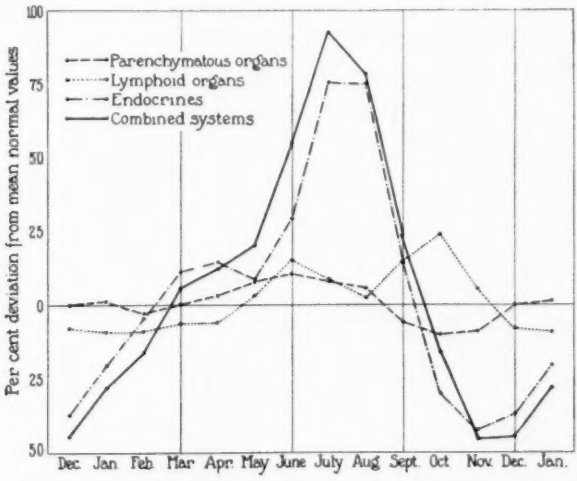

Chart 7.—Combined system values—aggregate organ balance.

It is thus evident that the relation between seasonal conditions and organ balance is not simple and quantitative. Moreover, the occurrence of variations in the weights of organs affects not only the organ-body weight relation, but the relation of one organ to another, or of one system of organs to another, so that the composition of the organ balance varies qualitatively as well as quantitatively.[3] For present purposes, this phase of constitutional variation may be illustrated by the relation between the endocrine and lymphoid systems expressed as a ratio. It is found that this relation varies in much the same way as the total organ balance, owing to the fact that the endocrine organs usually dominate the situation, but the variations in the lymphoid

3. Among the interrelations investigated by us, the only constant relation found is that between the pituitary and suprarenal glands.

system are sufficient to produce an appreciable effect on ratio values, especially during the critical periods of spring and fall.

It must not be assumed, however, that the variations in organ balance repeat themselves in a perfectly methodical manner year after year. This is not the case. The time of occurrence of seasonal

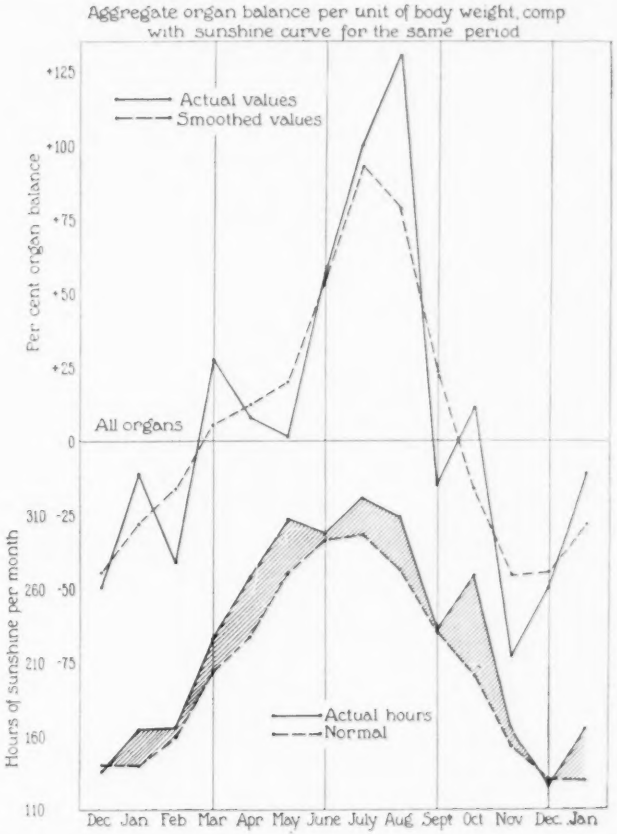

Chart 8.—Aggregate organ balance per unit of body weight, compared with sunshine curve for the same period.

variations and the magnitude of the values attained differ greatly, and the difference between years is just as important as the seasonal changes.

Constitutional differences are not confined to physical factors. There are also chemical differences, as shown by a study of the blood, and while it has not been possible to investigate this phase of the subject as in the case of physical constitution, the results are suggestive.

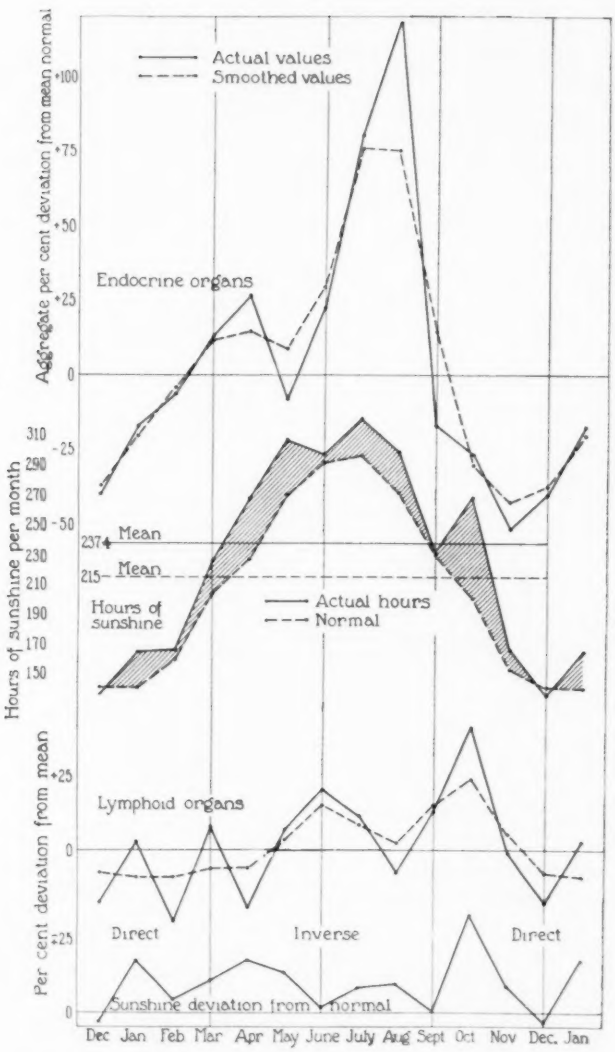

Chart 9.—Variations of organ balance in relation to sunshine.

These studies have been limited to four substances, serum calcium, inorganic phosphorus and the lipoid phosphorus and cholesterol of whole blood. For convenience in this discussion, lipoid phosphorus is estimated and spoken of as lecithin. The four substances mentioned form two couplets, the one organic and the other inorganic; taken

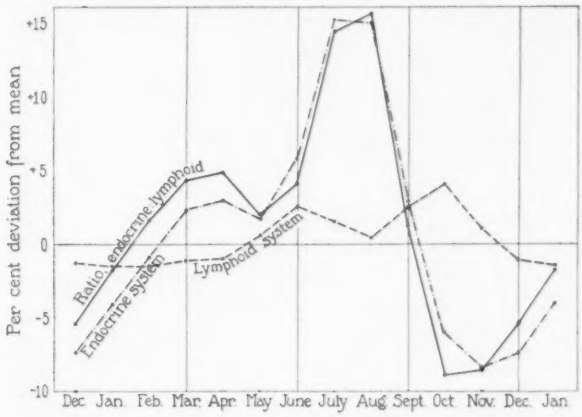

Chart 10.—Relation of endocrine to lymphoid system.

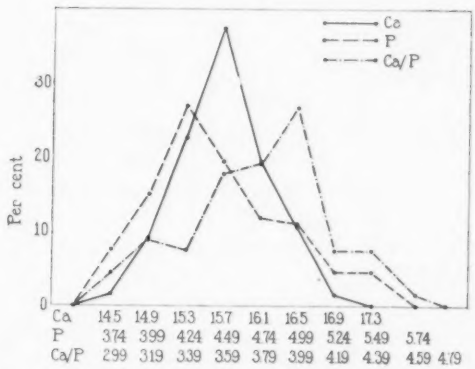

Chart 11.—Distribution of animals according to the mean levels of calcium, phosphorus and the calcium phosphorus ratio.

together, they present an interesting series of variations under normal and pathologic conditions which appear to be related to physical constitution on the one hand, and to environmental factors on the other.

While the methods available for the determination of these substances in large series of animals are not sufficiently accurate to enable

one to draw conclusions from a comparison of single values (unless the differences are large), the results of repeated determinations, or of group determinations, may be used as unit values.

To begin with, individual animals differ with respect to the mean levels of calcium, inorganic phosphorus, lecithin and cholesterol which they maintain in the blood just as they do with respect to the weights of organs or of any physical character. A classification of animals on this basis gives results which conform to the rule of thumb ratio of 1:3:1. This is shown by the distribution curves for sixty-eight animals based on the mean levels of calcium, inorganic phosphorus and the calcium-phosphorus ratio, as determined by systematic observations over a period of from four to eight months.

The concentration of these substances in the blood is also subject to frequent variation with a seasonal change of level. An example of the kind of conditions that may be expected is furnished by results obtained between October, 1927, and September, 1928 (charts 12 and 13). It cannot be assumed that these results represent the normal expectation, as conditions which prevailed during the period covered by these observations were distinctly abnormal (note sunshine curve). It appears, however, that the seasonal variation is more clearly defined among animals living outdoors than among those in the laboratory. In fact, the change from outdoor to indoor life may be sufficient in itself to induce alterations in the chemical composition of the blood which will completely obscure the seasonal variation.

The effect of these changes on the relation of one substance to another is of especial interest: for example, inorganic and lipoid phosphorus. Between these two substances there is an almost perfect inverse relation; as a rule, when one increases, the other diminishes, while their sum tends to remain constant. In summer, it is the inorganic component that is high, while in winter the lipoid fraction is high and the inorganic low. These relations hold not only for seasonal variations, but under a variety of conditions, and probably play an important rôle in such diseases as rickets.

Cholesterol and calcium also show a high correlation of the inverse order. Going still further, one finds that the ratio between cholesterol and calcium varies inversely with the ratio between lecithin and inorganic phosphorus, so that even small variations in the absolute amounts of these four substances are sufficient to produce marked changes in equilibrium with characteristic seasonal differences. Thus, it appears that in winter the ratio of cholesterol to calcium is lower than the ratio of lecithin to inorganic phosphorus, while in summer this relation is reversed.

Other conditions could be cited, but this is sufficient to show that there are variations in the chemical composition of the blood which are

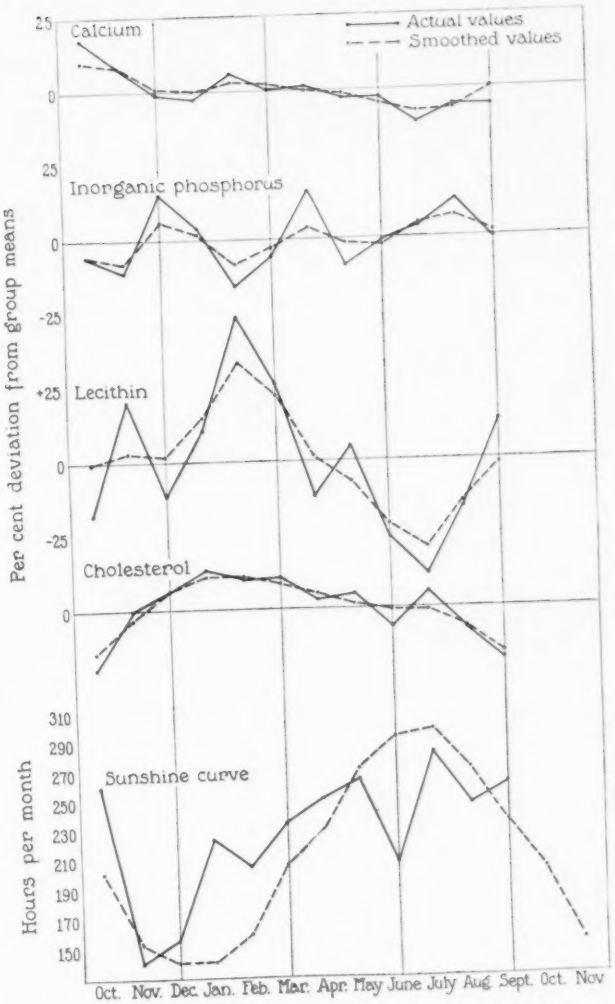

Chart 12.—Variations in the chemical composition of the blood of animals when first brought into the laboratory.

of the same general order as the variations in physical constitution. Similar studies have been made on the cellular elements of the blood, and while I am not prepared to discuss this phase of the subject at present, it seems that the results obtained will fit into the general scheme of behavior of other factors.

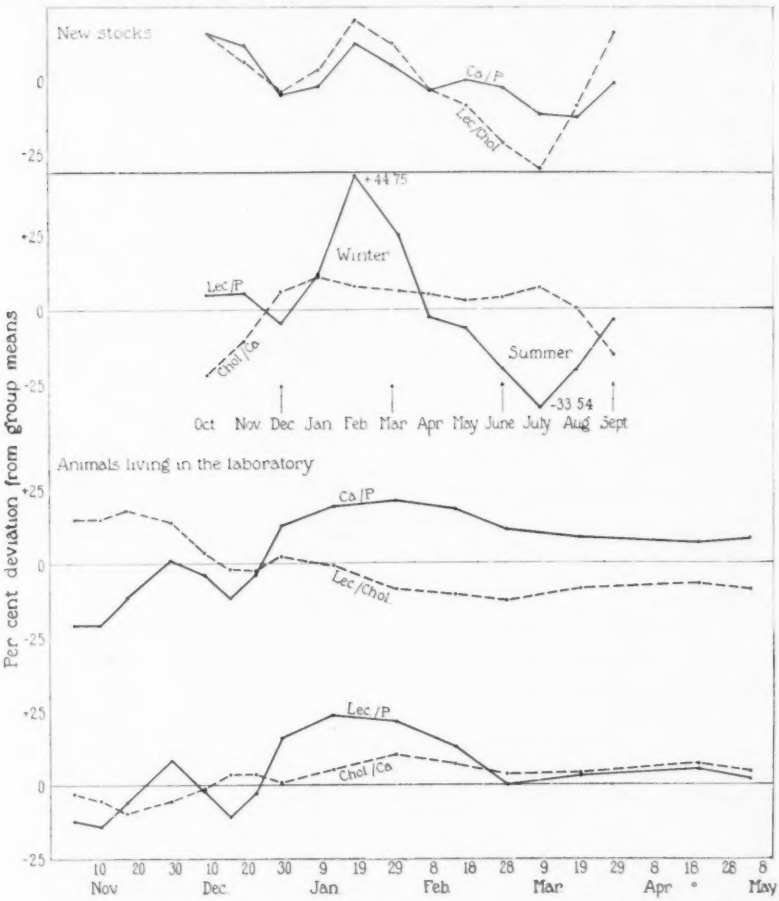

Chart 13.—Variations in the relations of calcium, inorganic phosphorus, lecithin and cholesterol in the blood.

At this point, attention may be called to the fact that in analyzing the results of a system of chemical variation as simple as that with which we have worked, there is abundant evidence to show that chemical constitution is a matter of total concentration and relation, just as in the case of organic constitution, and that, if sufficient data

were available, chemical constitution might be reduced to an expression comparable with that used for organic constitution. This is of especial interest in connection with variations in susceptibility to disease and in the reaction to disease. An excellent example of this condition is furnished by rickets.

So far, I have dealt with organic and chemical variations that are presented by animals as they are brought to the laboratory (chemical)

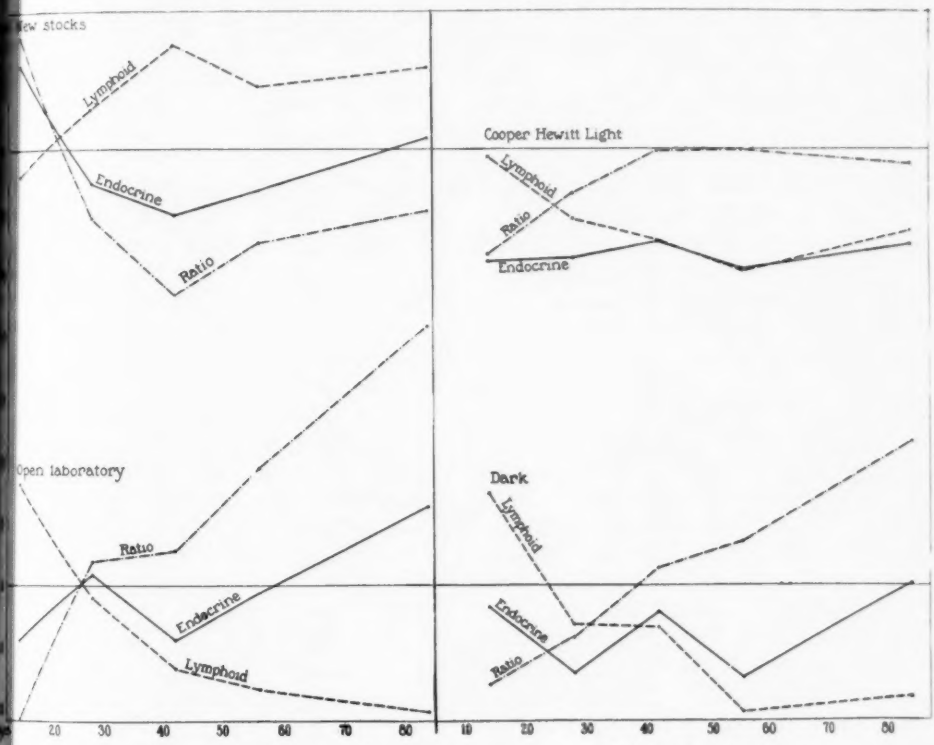

Chart 14.—Influence of light environment on equilibrium of endocrine and lymphoid systems.

or within a short time thereafter (organic constitution). It has been pointed out, however, that in addition to certain inherent differences in the constitution of animals, variations occur which suggest a relation to environmental factors such as sunlight. This, of course, does not imply that the relation to other factors is not equally close, but merely that there is a suggestion of a light relation. The influence of light on organic phosphorus is familiar to all, but less is known concerning

the effect of light on other constituents of the blood and very little as to its effect on physical constitution apart from phenomena of nutrition and growth, but it can be shown that light environment is capable of producing definite effects on both the physical and the chemical constitution.

The effect on organic constitution may be illustrated by a comparison of concurrent results obtained for several groups of animals living under different environmental conditions. These results may be compared on the basis of the values obtained for organ systems rather than those for given organs, and with especial reference to the ratio of endocrine to lymphoid tissues. There are four conditions to be considered: (1) exposure to winter sunlight (outdoors); (2) exposure to filtered sunlight of the laboratory; (3) constant exposure to light from Cooper Hewitt lamps (low pressure mercury arcs in crown glass), and (4) exclusion of all light. Two of the conditions are subject to irregular variation; the others are fixed so far as the light is concerned. From time to time animals from each of these groups were killed and the organs weighed.

The weights of endocrine and lymphoid organs of animals exposed to unfiltered sunlight varied in such a way as to cause first a marked reduction and then a slight increase of ratio values, but the ratio remained subnormal. The changes that occurred among animals in the open laboratory and among those in the dark, however, were in the opposite direction and the ratio was increased to a point well above the mean normal level (standard value). The change under open laboratory conditions was greater than that in the dark. The outstanding feature of the effect produced by the Cooper Hewitt light was the establishment of an essentially normal equilibrium which was maintained for a considerable time despite the occurrence of variations in both systems of organs.

This effect of light environment on organic equilibrium is of especial interest because chemical equilibria are affected in a similar manner. This is clearly shown by the influence of light on blood calcium and inorganic phosphorus (chart 19). Among animals exposed to sunlight, calcium and inorganic phosphorus vary so that, other conditions being equal, the ratio of calcium to phosphorus is inversely proportional to the amount of light received. Of course, ultraviolet light is the prime but not the sole factor in determining these changes. When animals are brought into the laboratory and are thus deprived of ultraviolet radiations, two things happen. In the first place, the change in the mode of living produces a disturbance of equilibrium. When the effects of this influence have subsided, however, inorganic phosphorus tends to decrease, while calcium usually increases, so that

the ratio of calcium to phosphorus increases just as the ratio of endocrine to lymphoid tissues increases under similar circumstances.

If animals are exposed to Cooper Hewitt light or to the long wave length radiations of neon light, the increase in the ratio of calcium to phosphorus may be appreciably diminished, and there is a tendency to

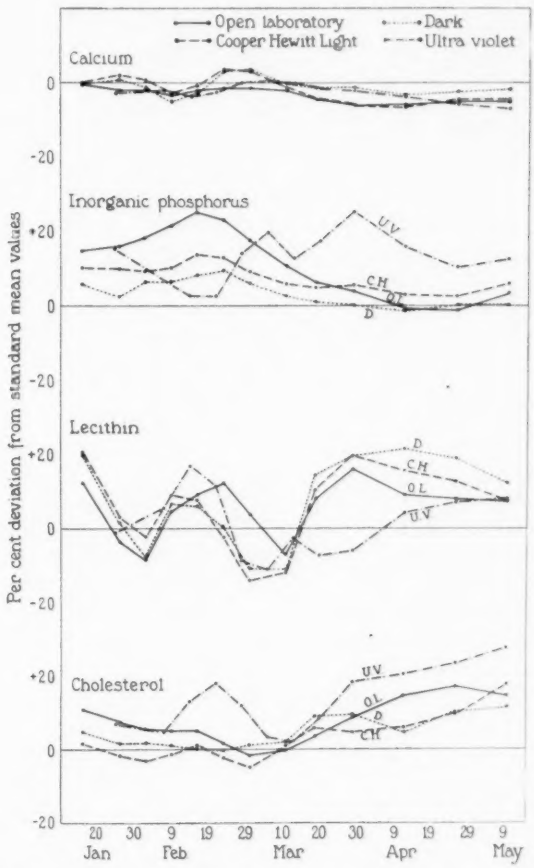

Chart 15.—Influence of light on chemical composition of the blood.

preserve a more uniform level. Animals in the dark, on the other hand, show an accentuation of the decrease in inorganic phosphorus and an increase in calcium with a higher ratio between the two substances. These effects are comparable with those on organic constitution and they are also comparable with differences found in animals of different ages.

The influence of light on the lecithin and cholesterol content of the blood and on the ratios of these substances to inorganic phosphorus and calcium is even greater (chart 15). For example, it was found that animals irradiated with the quartz mercury arc, at considerable distances (4.5 meters) and without removal of hair, showed an increase of inorganic phosphorus, a decrease of lipoid phosphorus, an increase

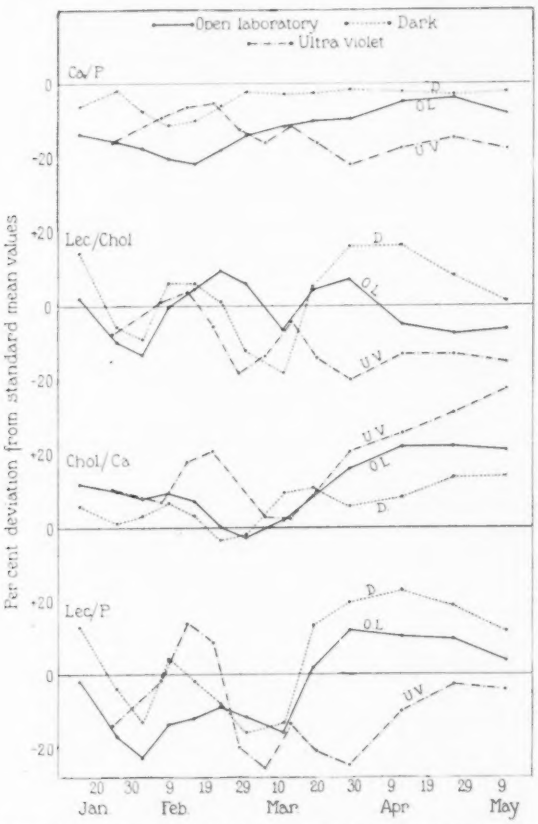

Chart 16.—Influence of light on chemical equilibria in the blood.

of cholesterol and a decrease in calcium. Complete exclusion of light had an opposite effect, while exposure to diffuse filtered sunlight or to Cooper Hewitt light produced intermediate results.

Similar conditions obtained with respect to ratio values (chart 16). In all cases, opposite effects were produced by ultraviolet irradiation and darkness. Thus, under the influence of ultraviolet light, the ratio between lecithin and inorganic phosphorus decreased while the ratio of

cholesterol to calcium increased, simulating conditions which prevail in summer, while exclusion of light produced an opposite effect with the development of conditions more analogous to those of winter.

It is extremely difficult to establish a mathematical correlation between the effects produced by environmental influences on physical and on chemical constitution owing to the limitations of methods now available. There is definite evidence of the existence of such a relation, but for the present it seems best to let the matter rest on the basis of analogy.

EFFECT OF PHYSICAL AND CHEMICAL CONDITIONS ON SUSCEPTIBILITY TO DISEASE

I come now to the question as to whether such physical and chemical conditions as those described have any bearing on susceptibility to disease. In the study of this problem, two chronic diseases have been used, syphilis and neoplasia. These diseases offer some advantages over the more acute infections. In the first place, they present every gradation in the severity of disease from an extremely mild to a uniformly fatal condition, and the clinical course of disease can be followed with reasonable accuracy from the time of inoculation to its conclusion. An opportunity is thus afforded for a comparison of many phases of the reaction over a considerable period. Variations in the course of disease can be measured qualitatively and quantitatively, in terms of the rate of progress of the disease or of the frequency of occurrence of a given condition, or in terms of the number and distribution of lesions of a given type. Moreover, while the incubation period of primary lesions may be influenced by dosage or by the growth activity of the cells or organisms used for inoculation (which in reality is a matter of dosage); the subsequent course of events is not affected by slight differences in these conditions. It is thus possible to eliminate the troublesome factor of dosage and to reduce the problem to the basis of factors represented by the host, on the one hand, and the pathogenic properties of the causative agent on the other. It makes no difference whether one regards the results of the interaction between these two sets of factors as an expression of susceptibility, of resistance or of virulence; the term used does not affect the results, and one's interest, for the present, is in the results and the relation of these results to known constitutional conditions.

Bearing this in mind, I shall consider what happens when animals are inoculated with *Treponema pallidum*. To begin with, there is a variable period of incubation; then a lesion develops at the site of inoculation and for a time increases in size. The growth of these lesions then ceases; some show a sudden development of edema followed by retrogressive changes, constituting a critical reaction, while others remain stationary or undergo partial resolution without crises. At any rate,

there is a period of quiescence or inactivity, constituting a second incubation period; then generalized or secondary lesions appear in some animals but not in others. Finally, all lesions undergo resolution, the animal recovers and the infection becomes latent. There are, thus, two

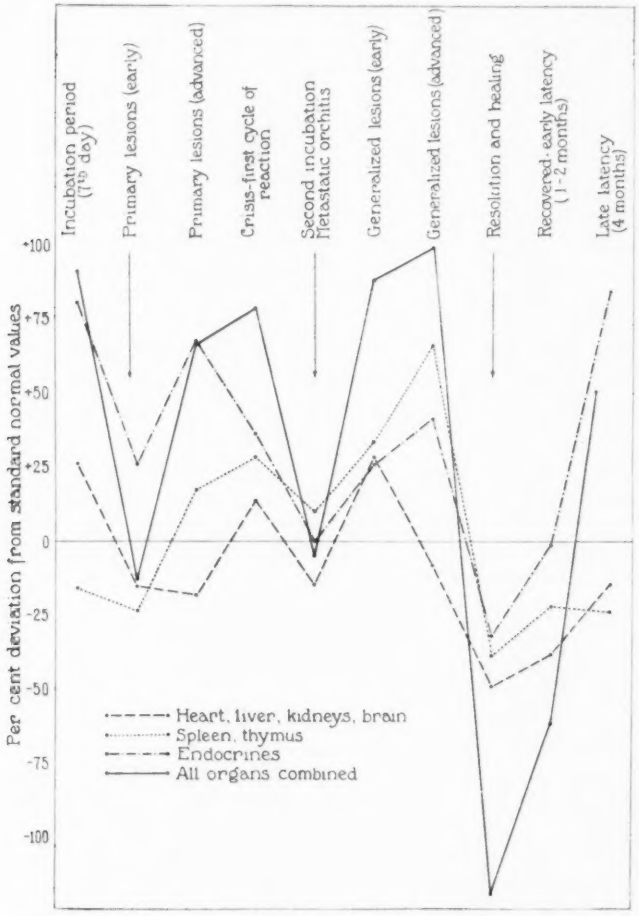

Chart 17.—Organ balance in experimental syphilis of moderate severity—aggregate values.

or more periods of development of the lesions, two or more periods of incubation or quiescence and two or more periods of resolution, marking the development of immunity and the termination of the active course of disease.

This is the clinical course of events, but there are equally striking changes in physical constitution which affect the organ-body weight relation on the one hand, and the relations between organs on the other (charts 17 and 18). The changes in physical constitution parallel the clinical course of disease throughout, with periods of increasing and decreasing organ balance corresponding with the periods of activity and quiescence of lesions, and terminate with the development of a state of organic equilibrium in the immune animal which differs from that

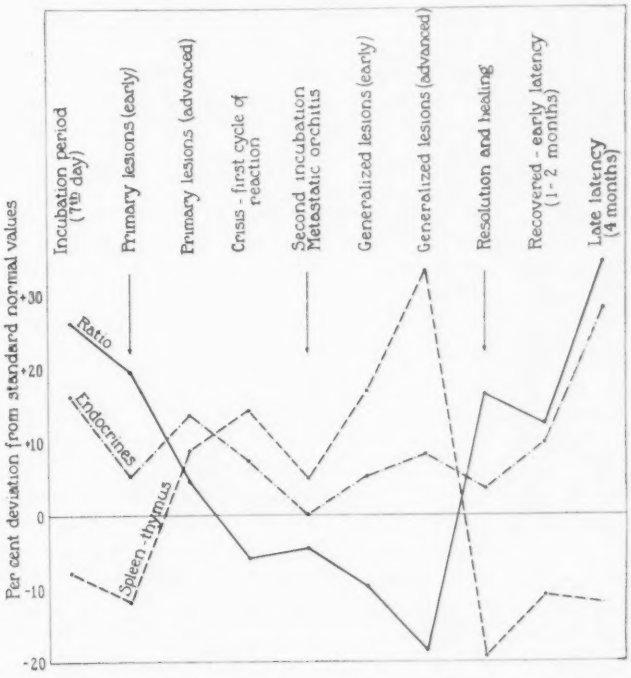

Chart 18.—Endocrine-lymphoid equilibrium in the reaction to syphilitic infection.

of the normal animal. The exact nature and extent of the change that occurs vary with the severity of the disease. Since visceral lesions do not occur in rabbits, these changes must be regarded as systemic reactions to infection.

In the case of the tumor, inoculations are made with a homogeneous cell emulsion, but the results are extremely variable. Some animals are completely refractory, others develop a benign tumor, while still others develop tumors which metastasize to all parts of the body and kill within from three to four weeks from the time of inoculation.

Animals with tumors show a series of changes in organic constitution analogous to those seen in syphilis. Thus, in the case of animals with benign tumors and of animals that recover, there is a tendency to develop a strongly positive organ balance, while in animals with malignant tumors, the balance becomes negative.

In this connection, it is of interest to note that animals which are immune to one of these diseases show an increased resistance to the other and, conversely, animals which are highly susceptible to one disease are highly susceptible to the other; that is, a classification of animals on the basis of susceptibility to one disease holds also for the other.

A similar situation obtains with respect to changes in the chemical composition of the blood. In this instance, I wish to emphasize especially the importance of changes which lie entirely within the so-called limits of normal and are usually regarded as of no significance. An interesting example of this condition is furnished by the calcium-phosphorus equilibrium in the reaction to syphilitic infection (charts 19 and 20). The points to which I wish to direct attention are: (1) the relation between the development of lesions as manifestations of the state or progress of the reaction to infection and the occurrence of changes in the chemical composition of the blood at corresponding times, especially at the time when new lesions cease to appear; (2) the difference between the calcium-phosphorus equilibrium of animals that have suppressed their infection and normal animals living under the same conditions.

As I have already pointed out, one cannot grasp the full significance of such changes as those seen in these experiments without considering both concentration and relation. It may be seen, however, that the trends of the curves for inorganic phosphorus and for the calcium-phosphorus ratio in particular show a definite relation to the course of disease. It is also of interest to note that the precise nature of the change differs somewhat with conditions that exist at the time of inoculation, with the severity of the disease and with the conditions under which the animals are living. The changes that occur during the early stages of the infection are variable, but as the progress of the disease is arrested, there is usually an increase in the calcium-phosphorus ratio which may be caused by either an increase in calcium or a decrease in inorganic phosphorus. This is followed almost immediately by a reversal of the direction of these curves; inorganic phosphorus increases and the calcium-phosphorus ratio decreases so that in the immune animal not only are the values obtained for calcium and phosphorus nearer the mean normal levels than those for normal animals living under the same conditions, but they show less fluctuation.

The results as here presented are for groups of ten animals each. The relation between the course of disease and the chemical composition of the blood is brought out much more clearly by comparing the results for individual animals, but it is not obscured by grouping the results despite the fact that the course of disease in different animals is variable and the changes in the blood of one not infrequently counterbalance those of another.

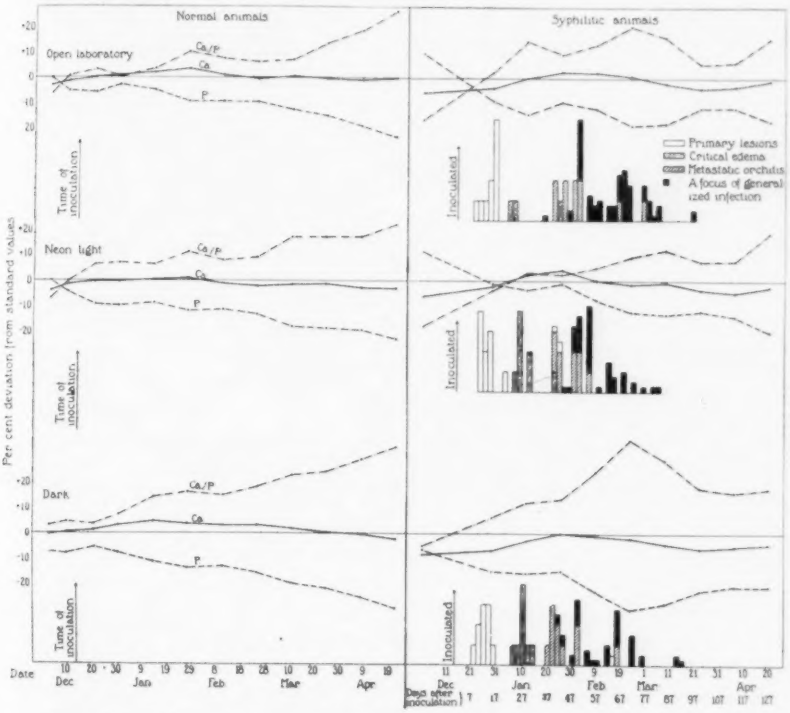

Chart 19.—Relation between the course of syphilitic infection and the phosphorus equilibrium in the blood under different environmental conditions.

It is not certain whether the changes in the calcium-phosphorus equilibrium are to be regarded as direct results of the reaction to infection or are referable to changes in other substances, such as lecithin and cholesterol, which show an even greater response.

In animals with tumors, it is more difficult to establish a definite relation between chemical variations and the reaction to disease. Marked alterations are obtained in the composition of the blood with clearly defined differences between animals that recover and those that die.

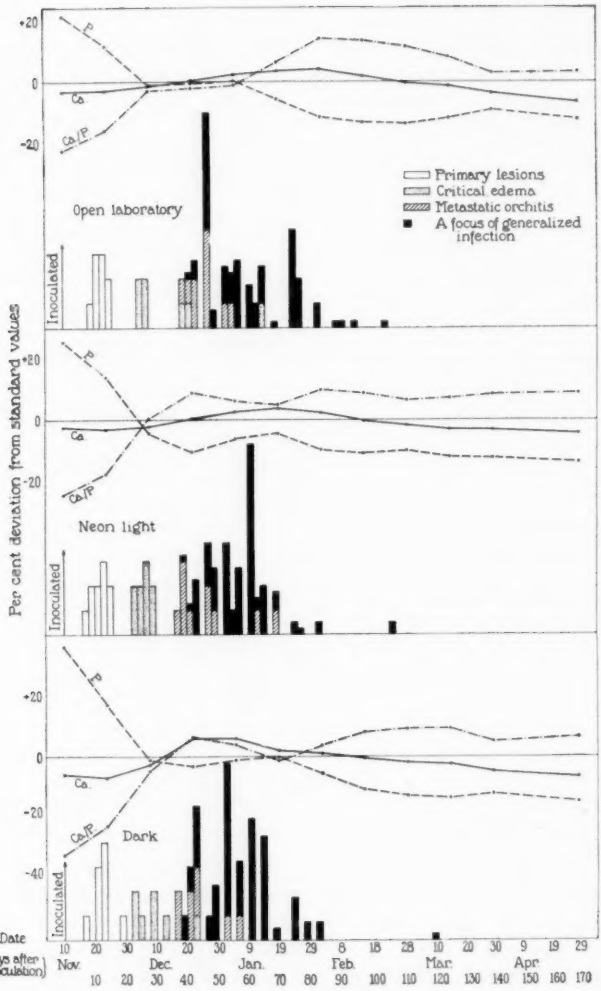

Chart 20.—Relation between the course of syphilitic infection and the calcium-phosphorus equilibrium in the blood under different environmental conditions.

but the interpretation of results is complicated by the localization of metastases in important organs. It can be said, however, that in the fatal cases there is a marked terminal increase in inorganic phosphorus and a decrease in calcium, with an increase in cholesterol and a decrease in lecithin; animals that recover show an opposite result.

The type of change that occurs in the blood of syphilitic animals, and apparently also in animals with tumor, is of especial interest in that the reaction of recovery shows a tendency to revert to and to maintain a form of equilibrium which is usually associated with a particular type of organic equilibrium, on the one hand, and with certain environmental influences, on the other, both of which are characterized by seasonal prevalence and comparatively low susceptibility. It is surprising that, merely by the use of systematic observations, differences of the magnitude of those concerned in most of these reactions can be shown to bear such a close relation to a reaction to disease. After all, it is not the magnitude of a result that determines its significance but the relation which a result bears to something that is known to be significant.

Reversing the order of procedure, it has been found that the course of disease may be influenced in a definite direction by the use of measures which disturb organic equilibrium directly, as by the removal of a part or the whole of some organ, or by interference with the coordinating mechanism. Thus, removal of the thyroid greatly increases the malignancy of the tumor and the severity of syphilitic infections, but removal of only a part of the thyroid produces an opposite effect, while extirpation of ganglions or of parts of the nerves of the cervical sympathetics also affects the course of disease.

In like manner, the course of disease may be affected favorably or unfavorably by chemical agents which act not on the parasite but on the host, such as the iodides, or by the use of conditions which involve nothing more than a difference in light environment. As I have pointed out, light affects both physical and chemical constitution in a manner which, under certain circumstances, might be expected to increase the severity of disease and under other circumstances, to diminish it. As will be seen later, the results obtained agree with expectations based on the assumption of a constitutional effect of light.

ACTUAL RELATIONS BETWEEN CONSTITUTIONAL STATES AND SUSCEPTIBILITY TO DISEASE

So far, I have discussed variations in physical and chemical constitution of individual animals and of animal populations, the effects of disease on constitution and the effects of constitutional disturbances on disease. I come now to a consideration of the actual relations that obtain between given constitutional states, on the one hand, and

susceptibility to disease, on the other, as measured by the incidence and severity of reaction phenomena.

I shall consider the distribution of various types of reaction among syphilitic animals, using the occurrence of generalized lesions as the basis of classification. In my experience, the incidence of generalized syphilis in rabbits varies from about 20 to 100 per cent, with a mean of approximately 60 per cent (unilateral testicular inoculation with the Nichols strain of *T. pallidum*.) The number of lesions or foci of infection is also variable, so that by actual count a numerical classification of animals can be made which corresponds with the extent of the lesions presented.

If the incidence of generalized syphilis is used as the basis of classification, animals are divided into two groups. As approximately 40 per cent of all animals show no generalized lesions, the reaction displayed by these animals is not measurable on this basis; they are, so to speak, submerged. The remaining 60 per cent, however, give a distribution curve comparable to the diminishing segment of a normal bell-shaped curve which suggests that if the reaction of the submerged fraction could be classified accurately, the resulting distribution would be much the same as that for organ weights or for other physical or chemical characters (chart 21, *A*).

Since, at times, the incidence of generalized syphilis does reach 100 per cent, it is possible in such instances to classify the reaction of all animals, and when this is done one finds that the distribution curve is in reality a normal curve with a positive skew and is of the same order as the curves for constitutional distribution with the same 1:3:1 ratio (chart 21, *B*). By comparing the curve based on mean susceptibility with the curve for high susceptibility, one finds that the main difference is in their position on the susceptibility scale. Experience has shown that the distribution of persons about the mean or mode does not vary with the severity of the disease. During periods of transition, the scatter is increased, but the group as a whole is moved up or down as the case may be.

This analysis brings out two important points: (1) that the factor of susceptibility is distributed in accordance with the same principles that govern the distribution of physical and chemical characters and (2) that the distribution curves for susceptibility and constitution are of the same type as the so-called epidemic curve.

An analysis of the variations of group reactions is also instructive. The signficance of the occurrence of periodic increases and decreases in the severity of disease may be shown by a comparison of the results obtained for tumor malignancy and organ balance covering the same period. As a matter of fact, the animals used for the two sets of experiments were taken from the same stock—one lot was killed for a study of organ weights, the other was inoculated with the tumor.

Tumor malignancy may be reduced to the basis of a simple numerical expression by the use of two factors, namely, the incidence of metastases or of malignant tumors among the animals of a group and the extent of the metastatic involvement. The latter condition is determined at autopsy by a systematic enumeration of the organs and parts of the body in which metastases occur.

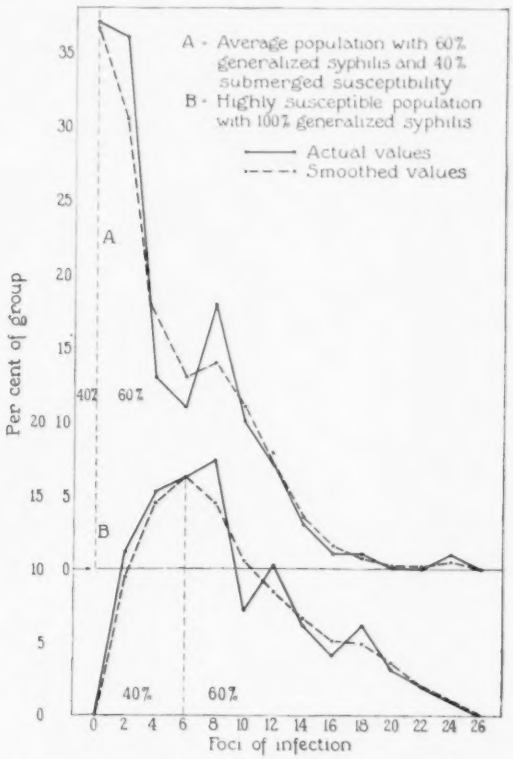
A - Average population with 60% generalized syphilis and 40% submerged susceptibility
B - Highly susceptible population with 100% generalized syphilis
Actual values
Smoothed values
A
B
40%
60%
40%
60%
Per cent of group
Foci of infection
0 2 4 6 8 10 12 14 16 18 20 22 24 26
35 30 25 20 15 10 5 0 5 10 15 20

Chart 21.—Distribution of individual susceptibility to syphilitic infection.

If the results for the three years are reduced to the basis of a single year, as was done in the case of the weights of organs, it is found that both the incidence and the distribution rates show distinct seasonal variations with high points in the late winter, early spring and fall; the values for the summer months are much lower (chart 22). It will be noted, however, that the high and low points of the two curves do not coincide, but a change in one tends to precede a change in the other, indicating that there is some difference between the factors of prevalence

and severity. True malignancy is expressed more accurately by a combination of the values for incidence and distribution.

The curve obtained in this way does not differ greatly from the mortality curve for New York covering the same period and including deaths from all causes (chart 22). Both curves may be regarded as measures of vitality, and they agree in indicating that vitality is higher

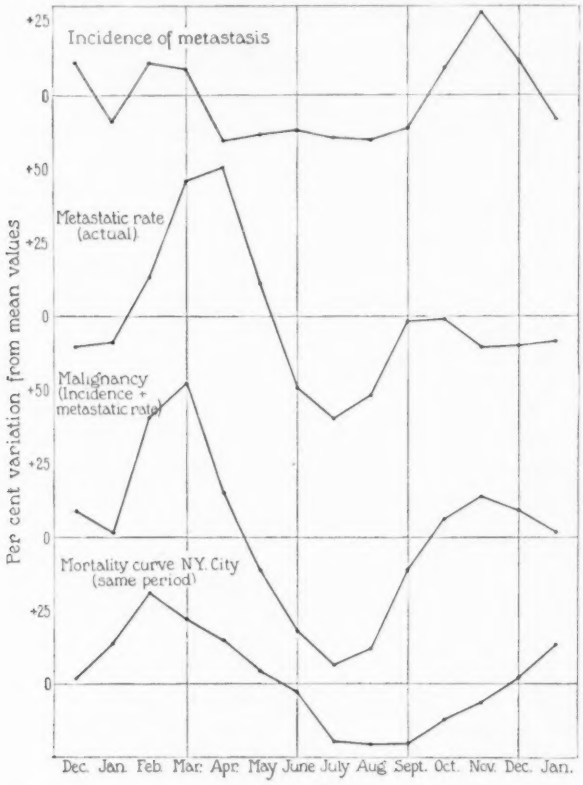

Chart 22.—Susceptibility to a transplanted tumor. Combined results for from 1922 to 1924.

during summer than at other times. This is precisely what would be expected if one assumes that vitality is a function of organic constitution, as may be seen by a comparison of the curves for organ balance and malignancy (chart 23). In some respects, the results given by actual values are even more striking than those shown by smoothed values.

These two curves epitomize a situation which cannot be dismissed as mere coincidence—they present actual conditions. On the one hand, there are facts concerning the reaction of animals to inoculation of

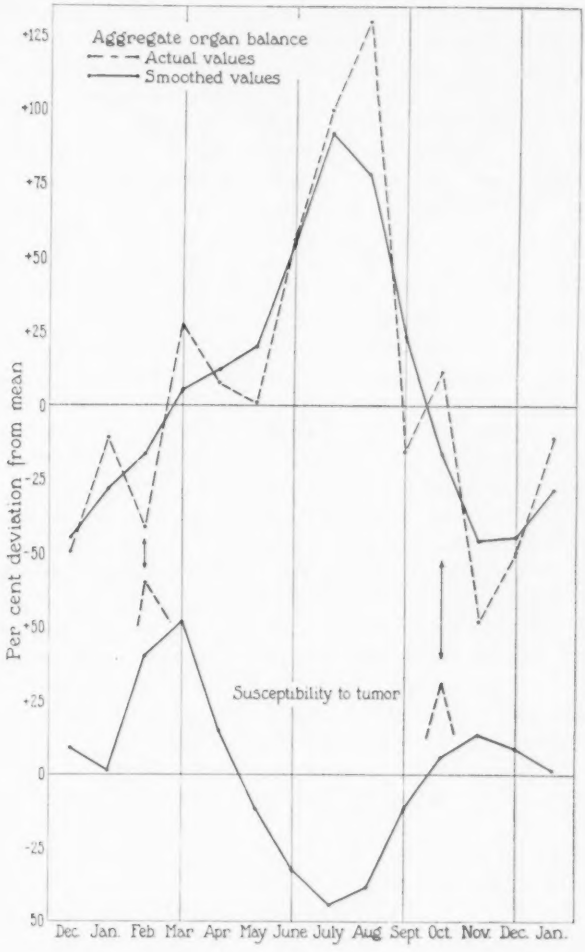

Chart 23.—Organ balance and malignancy. Concurrent determinations.

tumor and, on the other, results for organic constitution based on animals taken from the same stocks. Our results for the reaction to syphilis are not so complete, but as far as the critical periods are concerned, they are in essential agreement.

So far, I have dealt with facts which could be ascertained by the use of simple methods of precision. I shall now consider the meaning of these facts. It has been found that organic constitution, chemical constitution and the reaction to disease are all variables which are distributed among an animal population in essentially the same manner, and that while the relative distribution of these characters within the group is virtually constant, the values for groups as a whole are subject to wide variation. It has also been found that constitution in its broadest sense and the reaction to disease show clearly defined seasonal variations of the same general order and that variations of a similar character can be produced experimentally by changing the mode of life of animals or by changes of environment. Furthermore, it has been found that disease gives rise to changes in physical and chemical constitution comparable with those that occur in normal animals at different periods of the year or with variations in susceptibility to disease and, conversely, that disturbance of the normal constitutional equilibrium gives rise to decided changes in the efficiency of the reaction to disease. It has also been found that the changes in physical and chemical constitution, metabolic activity and susceptibility to disease which are produced by environment are of the same nature as the differences presented by animals of different age groups; that is, the effects of environment and of age are expressed in a similar manner, so that the comparison of the ages of man with the seasons represents something more substantial than poetic fancy.

In brief, it would appear that in all these conditions one is dealing with two sets of factors, the one physical or chemical and the other functional, and that these factors are so intimately related that a variation in one is always reflected by a variation in the other. In other words, it seems that the reaction to disease is essentially a functional expression of a physicochemical status. According to this conception, the organs and tissues of the body are structural units which individually and collectively perform or control the functional activities of the body. The reaction to disease is as much a functional activity of the body as the processes of digestion and assimilation, and I know of no reason to regard the reaction to disease as more highly specialized than the performance of any other vital function.

The question now arises as to whether conditions that obtain among experimental animals throw any light on the relation of man to disease. The answer to this question is indicated by a comparison of the experimental results with the mortality curve for New York covering the same period. But, in attempting to apply the results of these experiments to human constitution and susceptibility to disease, differences in behavior are to be expected. Moreover, there are certain conditions that must be taken into account.

In the first place, a distinction must be drawn between a constitutional status as it affects general health and vitality and a status which is favorable or unfavorable for the development of a particular disease. While at present knowledge is limited to conditions which affect susceptibility as a general proposition or susceptibility to certain experimental diseases, there are definite indications of the manner in which specific susceptibilities may be affected. There are two phases of organic constitution to consider, namely, the organ-body-weight relation or organ balance and the organ equilibrium or interrelation of organs. The basic relations of these states differ in persons by virtue of inheritance; they vary from month to month and from year to year in response to certain environmental influences. There is, however, a normal trend. In summer, the tendency is toward a high positive organ balance with a predominant endocrine influence; in winter, this condition is reversed; spring and fall are periods of transition. Moreover, the change from a summer to a winter status is accomplished, as a rule, by a rapid but continuous transition from the maximum level of July or August to a minimum level in November. The transition from winter to summer conditions, however, is irregular and discontinuous with a tendency to reverse movements; as a rule, the greatest irregularity occurs during February and March. This is merely an ebb and flow of a seasonal tide in the animal organism comparable with that in plants and subject to the influence of environmental conditions.

In estimating the bearing of these conditions on susceptibility, one must consider the form and level of constitutional values, the stability and the rate and smoothness of transition from one state to another. As I have already pointed out, high values are favorable and low values are unfavorable, but transition in either direction is a disturbing influence. This is particularly true of movements in a direction opposite to that of the normal trend. If the movement is gradual and continuous, incidence is affected more than the severity of the disease, but if the movement is rapid, irregular or extreme, the severity of the disease is increased accordingly. Thus, in the malignancy curve, the fall increase is due largely to an increase in the proportion of animals with malignant tumors, while the spring rise shows a greater increase in the distribution of metastases or in the actual malignancy of the tumor.

This phase of constitutional variation has a probable bearing on the seasonal prevalence of disease but, here again, a distinction must be drawn between acute and chronic diseases. I have worked entirely with chronic diseases, but in one case (tumor) the ultimate course of disease is usually determined within from two to four weeks after inoculation, while in the other (syphilis) the period is from two to three months. So far as the general trend of variations is concerned, the results for the two diseases agree, but, using the time of inoculation as the point

of reference, it has been found that susceptibility to the tumor was more closely related to prevailing constitutional and environmental conditions than susceptibility to syphilis; that is, the influence exerted at a particular time might be sufficient to determine the end-result in one case, whereas in the other, the time or length of action would be insufficient to produce a decisive effect, or the effect produced might be modified subsequently by the action of some other influence. The principle to be deduced is that the more acute the disease, the greater the influence of prevailing conditions and the greater the effect of abrupt or radical deviations from prevailing or normal conditions.

There is still another feature of this conception which should be made clear. In an effort to arrive at a few general principles, the results of these experiments have been condensed to the basis of a single year, while in reality they cover a period of several years. A comparison of results for different years shows that while variations in constitution and susceptibility tend to follow the same general trend from year to year, the time and extent of the variations may differ greatly. Moreover, there is some experimental evidence to show that constitutional variations and susceptibility to disease follow a cycle of progressive increase and decrease extending over a period of years. These observations may have a bearing on variations in the prevalence and severity of disease from year to year as well as the periodic recurrence of epidemics.

With reference to particular diseases, it is to be expected that conditions that are favorable for the occurrence of one disease may be unfavorable for the occurrence of another.[4] For, after all, pathogenic organisms must live and multiply in the body to produce disease. In this sense, the body is a culture medium, but all living things require appropriate conditions for their growth. Pathogenic organisms are not exceptions to this rule, and it will probably be found that the variations which occur in the chemical composition of tissues and fluids, independent of any specific immunologic reactions, are sufficient to account for wide variations in the prevalence and severity of particular diseases.

While I am not concerned, at this time, with the rôle of the causative agents of disease, attention may be called to the fact that if variations in dosage or virulence occurred in these experiments, they made no clearly defined impression on the results or else they followed the direction which I have ascribed to susceptibility and were subordinate to the influence of constitutional factors. This was to be expected since there are, after all, comparatively few infectious diseases which

4. Sydenham: The Works of Thomas Sydenham, M.D. Translated from the Latin Edition of Dr. Greenhill by R. G. Latham. Printed for the Sydenham Society, London, 1848, vol. 1, ch. 2.

terminate fatally in more than 50 per cent of cases; that is, in most instances, the ultimate balance of power rests with the host and not with the infecting organism. Moreover, it is not impossible that some of the conditions which one is accustomed to regard as changes in virulence may be nothing more than expressions of growth in a favorable or unfavorable medium. In this case, virulence and susceptibility become one and the same thing—a function of constitution. But; in presenting the matter in this way, it is not my intention to minimize the importance of variations in the pathogenic properties of micro-organisms or to deny the occurrence of variations independent of the host. On the contrary, it has been found that so far as *T. pallidum* is concerned, not only are there differences in the pathogenic properties of different strains, but the properties of a given strain can be changed materially by experimental means, such as continued propagation under favorable or unfavorable conditions.

COMMENT

So far as they go, my experiments not only are in harmony with known facts concerning human constitution and susceptibility to disease but they enable one to state some of the general principles of the constitutional concept in simple terms of present knowledge and to visualize conditions which may influence susceptibility to disease. Constitution thus becomes a concrete reality which lends itself to measurement and test in accordance with the demands of modern science. The elementary conception of constitutional variation and its relation to disease which I have attempted to outline involves only one assumption, and that is that all functional activities of the body are either performed or controlled by organs and tissues and that the organs are provided in such numbers and amounts as are necessary for the performance of their appointed functions. One need not know the function of a single organ in order to show that persons differ from one another in respect of their organic equipment, or that they are persons and not standard machines or standard mediums for the growth of pathogenic micro-organisms. It can be shown that variations in the mass and mass relations of organs are constantly occurring in response to demands made by changing conditions of life and that these variations in organic constitution are accompanied by variations in chemical constitution, all of which may well be confined within the usual limits of normal, for they are normal. It can also be shown that these differences and variations in physical and chemical constitution are associated with differences and variations in functional activity and susceptibility to disease or in the degree of natural immunity.

Changing conditions of life affect individuals and groups, but as individuals differ in respect of their inherent constitutional equipment, they differ also in their reaction to influences of all kinds. Some are

capable of immediate and complete adjustment and others are slow to respond or are incapable of adjustment, so that when the members of a group are subjected to a change in the conditions of life or are exposed to infection under favorable or unfavorable conditions, the response obtained varies according to the capacities of the individual. Hence, even now, there is some understanding of how and why one person differs from another in respect of the general property of susceptibility to disease and why it is that the susceptibility of persons and of populations is not fixed but varies from time to time, independent of any immunity that may be acquired through previous exposure to a given disease.

When one is able to base all experiments on material of known genetic constitution and thus link together the two factors of heredity and environment, one will be in a position to gain a much clearer understanding of these intricate problems.

THE PATHOLOGY OF THE PANCREAS IN NON-DIABETIC PERSONS

A STUDY OF ONE HUNDRED AND FIFTY-SIX CONSECUTIVE AUTOPSIES ON NONDIABETIC PATIENTS *

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BOSTON

In a recent article, Gibb and Logan [1] presented valuable data bearing particularly on pancreatic changes found at autopsy on 147 patients with diabetes mellitus. As their report was based on diabetic patients alone, it seems worth while to report the pathologic changes in a series of pancreases from nondiabetic patients.

The autopsies done on nondiabetic patients in this laboratory during 1928, a total of 156, form the basis of the present analysis. The anatomic causes of death range from acute conditions such as typhoid fever, pneumonia and postoperative pulmonary embolus to various chronic conditions, among which the late manifestations of carcinoma were frequent. Suffice it to say that only in rare cases were pancreatic changes an important factor in the clinical course or in the causation of death. The ages at death of these patients varied from 8 days to 87 years.

In all cases sections of the pancreas were studied after staining with eosin methylene blue (methylthionine chloride, U. S. P.) and with phosphotungstic acid hematoxylin. In all autopsies done in less than three hours post mortem (this constituted a considerable portion of the autopsies), Mallory's aniline blue stain, Masson's three color stains and the granule stains of Bensley, Lane and Ukai were resorted to. The fixation was ordinarily Zenker's fluid, but frequently Helly's fluid, Champy's fluid and Regaud's method of fixation were utilized.

In table 1, the occurrence of interstitial pancreatitis and lipomatosis is given by decades. This is contrasted with table 1 A, which is table 1 of Gibb and Logan with their column headed "Arteriosclerosis" omitted.

The material is more concentrated in the older age groups. Not only do our nondiabetic cases show the same tendency for interstitial pancreatitis to increase in frequency with advancing age as do those of Gibb and Logan,[1] but also the frequency, while distinctly less, is never-

* Submitted for publication, May 25, 1929.

* From the Pathological Laboratory of the New England Deaconess Hospital and Palmer Memorial Hospital.

1. Gibb, W. F., Jr., and Logan, V. W.: Diabetes Mellitus; A Study of One Hundred and Forty-Seven Autopsies, Arch. Int. Med. **43**:376 (March) 1929.

theless so great as to preclude considering this a characteristic diabetic lesion. In making the diagnosis "interstitial pancreatitis" all cases showing only slight fibrosis were passed over, and only those showing clearcut (though at times focal) increase in interacinar or interlobular fibrous tissue included in the tabulation. In scattered instances, this fibrosis was accompanied by round cell infiltration. The occurrence of this fibrosis in nearly one half of the nondiabetic patients in the older age group rules it out as a characteristic diabetic lesion.

How far one may consider interacinar fibrosis as a cause of atrophy of the pancreatic tissue is open to question. I believe that in the pan-

TABLE 1.—*Age Distribution According to Decades in Nondiabetic Patients*

		Interstitial Pancreatitis		Lipomatosis	
Age	Cases	Cases	Per Cent	Cases	Per Cent
0 to 10	3	0	0	0	0
11 to 20	2	0	0	0	0
21 to 30	3	0	0	0	0
31 to 40	4	1	25	0	0
41 to 50	31	3	9.6	6	19.3
51 to 60	46	16	34.7	13	28.2
61 to 80	66	32	48.4	17	25.7
81 to 90	1	1	100	1	100

TABLE 1 A (table 1 of Gibb and Logan).—*Age Distribution According to Decades in Patients with Diabetes*

		Interstitial Pancreatitis		Lipomatosis	
Age	Cases	Cases	Per Cent	Cases	Per Cent
10 to 20	12	1	8	0	0
21 to 30	15	4	26.6	0	0
31 to 40	16	7	44	1	6.3
41 to 50	36	23	64	8	22
51 to 60	45	29	64	20	44.4
61 to 80	23	15	65	12	52

creas, as in the liver, fibrosis is more frequently a result than a cause of injury to the parenchyma.

When lipomatosis is considered, there is some similarity of the data presented here to those of Gibb and Logan.[1] This change is absent in the younger age groups in both series. The occasional occurrence of extreme emaciation with depletion of almost all the stored fat of the body in cases of carcinoma has undoubtedly lowered the incidence of lipomatosis in my series. Whatever the mechanism of development of pancreatic lipomatosis may be in diabetic persons, in this series it is much more intimately related to the amount of body fat than to atrophy or fibrosis of the pancreas.

Even in the islands themselves the occurrence of abnormalities is not restricted to diabetes. Indeed, their occurrence in nondiabetic persons is a prerequisite if one considers insular changes the cause rather than the result of diabetes. Table 2 gives the frequency of lesions in the

islands and the occurrence of interstitial pancreatitis. With it is contrasted table 2 A (table 2 of Gibb and Logan [1]).

The preponderance of normal islands in this series is of course to be expected. Fibrosis of the islands may presumably be brought about by the same causes that produce interstitial fibrosis, and so the relatively high correlation of the two lesions in both series is to be expected.

The occurrence of hyaline islands in the pancreas of a nondiabetic patient was first pointed out by Ohlmacher,[2] and other cases have been reported in some detail by Cecil [3] and by Wright.[4] If one accepts hyaline degeneration of the islands as a cause rather than a result of diabetes, a

TABLE 2.—*The Incidence of Lesions in the Islands*

		Interstitial Pancreatitis	
	Cases	Cases	Per Cent
Normal islands	130	40	30.7
Pyknotic islands	2	1	50
Slight fibrosis	7	6	85.7
Moderate fibrosis	4	3	75
Marked fibrosis	1	1	100
Hyaline islands	3	1	33.3
Hemachromatosis	0	0	0
Hydropic degeneration (?)	2	0	0
Mitotic figures	2	0	0
Hemorrhage	1	0	0
Adenoma	2	0	0

TABLE 2 A (table 2 of Gibb and Logan).—*Effect of Interstitial Fibrosis on Island Cells*

		Interstitial Pancreatitis		Capsular Thickening	
	Cases	Cases	Per Cent	Cases	Per Cent
Normal islands	11	3	28	3	27
Pyknotic islands	15	7	46	3	20
Slight fibrosis	31	14	45	17	55
Moderate fibrosis	23	11	48	16	70
Marked fibrosis	25	16	64	16	64
Hyaline islands	30	22	73	16	58
Hemachromatosis	7	7	100	4	57

moderate number of cases must exist in which the lesion is not sufficiently marked to produce symptoms. In my series there are three such cases—1 per cent of the total number.

I have avoided the question of capsular thickening, as Gibb and Logan [1] did not state whether they had taken Otani's [5] type A as a norm

2. Ohlmacher, J. C.: The Relation of the Islands of Langerhans to Diseases of the Liver, with Special Reference to Carbohydrate Metabolism, Am. J. M. Sc. **128**:287, 1904.

3. Cecil, R. L.: Hyaline Degeneration of the Islands of Langerhans in Non-diabetic Conditions, Am. J. M. Sc. **147**:726, 1914.

4. Wright, E. W.: Hyaline Degeneration of the Islands of Langerhans in Non-Diabetics, Am. J. Path. **3**:461, 1927.

5. Otani, S.: Studies on the Islands of Langerhans in the Human Pancreas, Am. J. Path. **3**:1, 1927.

(the capsule made up of the basement membranes of surrounding acini) or the delicate, more or less complete connective tissue capsule frequently found about the islands.

SUMMARY AND CONCLUSIONS

1. The pancreatic lesions in 156 autopsies on unselected nondiabetic patients are summarized.

2. Practically any lesion found in the pancreas of diabetic patients can be duplicated in the pancreas of nondiabetic patients, though the frequency of occurrence of lesions of the islands is much less in the latter group.

3. Interstitial pancreatitis occurs too frequently in nondiabetic patients to be considered a characteristic lesion of diabetes.

4. In many cases lipomatosis is related to the amount of body fat.

5. It is impossible from a study of the pancreas to diagnose the presence or absence of diabetes.

CALCIUM STUDIES

IV. THE CALCIUM CONTENT OF CEREBROSPINAL FLUID *

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The calcium content of human cerebrospinal fluid has not been extensively investigated, but the general impression is that it is extremely constant in health and in the great majority of pathologic states. Halverson and Bergeim [1] and Pincus and Kramer [2] found the spinal fluid of human beings to average about 5 mg. per hundred cubic centimeters. Critchley and O'Flynn [3] found it to be 6.2 mg., practically constant at that figure and not varying characteristically in disease, with the exception of a fall in tetany and a rise in Froin's syndrome.

The present study consists of the determination of the calcium content of the cerebrospinal fluid of 240 persons. Sixty-eight may be classed as normal, the remaining 172 suffering with a variety of disorders which may be grouped under six headings: (1) pulmonary tuberculosis in various stages of extent and activity; (2) disturbances of an atopic nature, including bronchial asthma, mucous colitis, vasomotor rhinitis and angioneurotic edema; (3) syphilis, including also paresis, tabes and cerebrospinal syphilis; (4) acute meningeal and cerebral infections, such as suppurative meningitis, tuberculous meningitis and epidemic encephalitis; (5) mental and neurologic disorders, including imbecility, mental deficiency, epilepsy, dementia praecox, mania and arteriosclerotic and alcoholic dementia; (6) a miscellaneous group including pregnancy and paroxysmal dyspnea of undetermined origin.

CALCIUM DETERMINATIONS

The calcium determinations were made by the Clark-Collip modification of the Kramer-Tisdall method.[4] They are detailed in the accompanying table and may be summarized as follows:

* Submitted for publication, June 15, 1929.

* From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest, Jefferson Hospital.

1. Halverson, J. O., and Bergeim, O.: The Calcium Content of Cerebrospinal Fluid, Particularly in Tabes Dorsalis, J. Biol. Chem. **29**:337, 1917.

2. Pincus, J. B., and Kramer, B.: Comparative Study of the Concentration of Various Anions and Cations in Cerebrospinal Fluid and Serum, J. Biol. Chem. **57**:463, 1923.

3. Critchley, M., and O'Flynn, E.: The Calcium Content of the Cerebrospinal Fluid, Brain **47**:337, 1924.

4. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

Normal.—In sixty-eight essentially normal persons, the spinal fluid calcium varied from 4.52 to 5.50 mg. per hundred cubic centimeters.

Pulmonary Tuberculosis.—For sixty-three patients with pulmonary tuberculosis of varying extent and activity, the figures ranged between 4 and 7.75 mg. per hundred cubic centimeters. In none of these cases was tuberculous meningitis present. For thirty-six of this group the figures were within normal limits (from 4.5 to 5.5); for twenty-two they were above, and for five, below normal.

Calcium Content of Cerebrospinal Fluid in Sixty-Eight Normal Persons and in One Hundred and Seventy-Two Persons with Various Pathologic Conditions

Condition	Cases	Calcium*	Normal†	Above†	Below†
Normal	68	4.52-5.50	68	0	0
Pulmonary tuberculosis	63	4.00-7.75	36	22	5
Bronchial asthma	25	4.39-6.33	8	16	1
Paresis	19	5.21-6.65	3	16	0
Tabes	12	5.23-6.29	3	9	0
Cerebrospinal syphilis	4	5.43-5.71	1	3	0
Acute meningitis	5	5.05-6.50	1	4	0
Tuberculous meningitis	3	5.88-7.50	0	3	0
Encephalitis	3	5.82-6.90	0	3	0
Epilepsy	4	5.00-6.00	3	1	0
Imbecility	2	4.90-5.30	2	0	0
Mental deficiency	2	5.60-5.80	0	2	0
Mania	1	5.85	0	1	0
Dementia praecox	3	5.82-6.73	0	3	0
Arteriosclerotic dementia	3	5.03-6.53	1	2	0
Alcoholic dementia	2	5.95-6.63	0	2	0
Syphilis	7	5.25-6.66	1	6	0
Pregnancy	6	4.50-5.25	6	0	0
Mucous colitis	3	5.62-6.00	0	3	0
Vasomotor rhinitis	2	5.75-6.10	0	2	0
Vasomotor ataxia	1	5.56	0	1	0
Paroxysmal dyspnea	1	5.00	1	0	0
Angioneurotic edema	1	5.50	1	0	0

* Calcium values expressed in milligrams per hundred cubic centimeters.
† Number of cases in each group within, above and below normal limits.

Atopic Disturbances.—In twenty-five patients suffering with bronchial asthma the concentration of spinal fluid calcium varied from 4.39 to 6.33 mg. per hundred cubic centimeters. For eight of these the figures were within normal limits; for sixteen, above and for one, below normal.

Three patients with mucous colitis showed figures of from 5.62 to 6 mg. of spinal fluid calcium, all being above normal.

For two patients with vasomotor rhinitis and one with angioneurotic edema the figures were from 5.5 to 6.1 mg., one being the high limit of normal and two above normal.

Syphilis.—Seven patients with syphilis without demonstrable involvement of the central nervous system had concentrations of spinal fluid calcium of from 5.25 to 6.66 mg. per hundred cubic centimeters. One was within normal limits and six above normal. In nineteen cases of paresis the figures ranged from 5.21 to 6.65 mg., being normal in three and above normal in sixteen. In twelve cases of tabes the figures were

from 5.23 to 6.29 mg., being normal in three and above normal in nine. Four patients with cerebrospinal syphilis had calcium concentrations of from 5.43 to 5.71 mg., one being normal and three above normal.

Acute Local Infections.—The observations in the group with acute local infections were as follows: Five patients had meningococcus meningitis, with a spinal fluid calcium content of from 5.05 to 6.5 mg.; for one of these, the figures were normal and for four, above normal. Three had tuberculous meningitis, with a calcium content of from 5.88 to 7.5 mg.; all of these were above normal. Three had acute epidemic encephalitis and a calcium content ranging from 5.82 to 6.9 mg.; all were above normal.

Mental and Neurologic Disorders.—The group with mental and neurologic disorders includes four patients with epilepsy, two imbeciles, two with mental deficiency, one with mania, three with dementia praecox, three with arteriosclerotic dementia, and two with alcoholic dementia. The calcium values ranged from 4.9 to 6.73 mg. per hundred cubic centimeters, six being within normal limits and eleven above normal.

Miscellaneous.—In six cases of pregnancy of from three weeks to ten lunar months, the calcium values ranged from 4.5 to 5.25 mg., all within normal limits. One patient with paroxysmal dyspnea of undetermined origin had a calcium content in the spinal fluid of 5 mg., and one with vasomotor ataxia, 5.56 mg.

For sixty-seven of the 172 patients with a variety of disorders, the values for spinal fluid calcium were within normal limits; for ninety-nine they were above and for six below normal.

CONCLUSIONS

1. The calcium content of the cerebrospinal fluid of sixty-eight normal persons was found to be from 4.52 to 5.5 mg. per hundred cubic centimeters. These figures support the prevalent belief in the constancy of the spinal fluid calcium under normal conditions.

2. The calcium content of the cerebrospinal fluid of 172 patients suffering with various disorders was from 4 to 7.75 mg. per hundred cubic centimeters. If one considers the normal limits to be from 4.5 to 5.5 mg., sixty-seven of these were within normal limits, ninety-nine were above and six were below normal. There is evidently considerable variation in disease, the great majority of patients with inflammatory disease of the meninges and brain, those with atopic disorders and syphilis and many with pulmonary tuberculosis having concentrations of spinal fluid calcium well above the high limit of normal.

CALCIUM STUDIES

V. THE RELATIONSHIP BETWEEN THE CALCIUM CONTENT OF CEREBROSPINAL FLUID AND BLOOD SERUM *

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The growing interest in disturbances of calcium metabolism within recent years has stimulated investigation of the state of calcium in blood serum and its distribution in various body fluids. The cerebrospinal fluid has received particular attention since, if it is assumed that this fluid is a protein-free filtrate of blood plasma, its calcium content may be taken to represent the diffusible calcium of the blood.

The question arises as to whether the cerebrospinal fluid may be correctly regarded as a protein-free filtrate of blood plasma. The literature on this point has been extensively reviewed by Becht,[1] Weed [2] and Levinson.[3] Several arguments have been advanced in support of the belief that the fluid is formed by a secretory process. Petit and Girard [4] demonstrated an increased flow following the administration of pilocarpine, muscarine and ether. Cappilletti [5] found a diminished flow following the use of atropine and hyoscyamine. Similar results have been obtained by many investigators and have been adduced as proof of the secretory origin of the fluid. Mott [6] believed that vacuoles which he found in the cells of the choroid plexus were conclusive evidence of secretory activity of these cells. Dixon and Halliburton [7] claimed a hormone action for extracts of the choroid plexus which, injected intravenously, resulted in an increased flow of cerebrospinal fluid.

* Submitted for publication, June 15, 1929.

* From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest, Jefferson Hospital.

1. Becht, F.: Studies on the Cerebrospinal Fluid, Am. J. Physiol. **51**:1, 1920.

2. Weed, L. H.: The Cerebrospinal Fluid, Physiol. Rev. **2**:171, 1922.

3. Levinson, A.: Cerebrospinal Fluid, ed. 2, St. Louis, C. V. Mosby Co., 1923, p. 51.

4. Petit, L., and Girard, P.: Sur la function secrétoire et la morphologie de plexus choroides, Arch. d'anat. Micr. **5**:213, 1902-1903.

5. Cappilletti, S.: L'écoulement du liquide cérébro-spinale par la fistula céphalo-rachidienne en conditiones normales et sous l'influence de quelques médicamentes, Arch. ital. de biol. **36**:299, 1901.

6. Mott, F. W.: Oliver-Sharpey Lectures: Cerebrospinal Fluid, Lancet **2**:1, 1910.

7. Dixon, W. E., and Halliburton, W. D.: Cerebrospinal Fluid: I. Secretion of the Fluid, J. Physiol. **47**:215, 1913.

On the other hand, Hassin [8] brought forward evidence to show that the function of the plexus is not secretion. Whether or not absorption occurs here, as he believes, there is no apparent reason why secreting cells should contain vacuoles. According to Becht,[9] the condition of the cells of the choroid plexus as described during the period of supposed "secretion" is the exact opposite of that seen in actively secreting cells. The latter have an inner granular and an outer clear zone, with distinct nuclei, whereas in the former there is an outer granular and an inner clear zone, the nuclei being indistinct. Becht furthermore showed that all changes in spinal fluid outflow and pressure due to drugs can be traced to variations in intracranial venous and arterial tension, and concluded that there is no evidence that the fluid is formed by secretion. McClendon,[10] on physicochemical grounds, claimed that the fluid is an ultrafiltrate of blood plasma. The differences in chemical determinations of plasma and spinal fluid may be due to differences in diffusibility of the various constituents of the blood and to a variation between the rates of entrance and absorption of certain elements of the fluid.

Levinson [3] found the hydrogen ion concentration of blood and spinal fluid to be identical and summed up the situation by this statement: "The fact that nearly all constituents of the blood are present in the cerebrospinal fluid and that their physicochemical properties are practically the same would make one believe that the cerebrospinal fluid is a direct product of the blood."

In view of these facts, there appears to be sufficient justification for considering the spinal fluid calcium to be the diffusible calcium of the blood. Furthermore, there seems to be a satisfactory agreement between the figures for spinal fluid calcium and those for diffusible serum calcium as determined by actual diffusion experiments. Halverson and Bergeim [11] and Pincus and Kramer [12] found the calcium content of human cerebrospinal fluid to average 5 mg. per hundred cubic centimeters, or from 45 to 50 per cent of the blood serum calcium. This ratio is the same as that reported by Neuhausen and Pincus [13] and by

8. Hassin, G. B.: Histopathology of Brain Abscess, Arch. Neurol. & Psychiat. **3**:616 (June) 1920.

9. Becht, F.: Studies on the Cerebrospinal Fluid, Am. J. Physiol. **51**:1, 1920.

10. McClendon, J. F.: The Formation and Composition of Cerebrospinal Fluid, J. A. M. A. **70**:977 (April 6) 1918.

11. Halverson, J. O., and Bergeim, O.: The Calcium Content of Cerebrospinal Fluid, Particularly in Tabes Dorsalis, J. Biol. Chem. **29**:337, 1917.

12. Pincus, J. B., and Kramer, B.: Comparative Study of the Concentration of Various Anions and Cations in Cerebrospinal Fluid and Serum, J. Biol. Chem. **57**:463, 1923.

13. Neuhausen, B. S., and Pincus, J. B.: A Study of the Condition of Several Inorganic Constituents of Serum by Means of Ultrafiltration, J. Biol. Chem. **57**:99, 1923.

Updegraff, Greenberg and Clark [14] for diffusible calcium as determined by ultrafiltration experiments.

PRESENT INVESTIGATION

The present study consists of the determination of the calcium content of blood serum and cerebrospinal fluid withdrawn at the same time in each case from 199 different persons. Of these, sixty-eight were normal and 131 had various pathologic conditions. The spinal fluid calcium was considered the diffusible fraction of the serum calcium,

TABLE 1.—*The Calcium Content of the Blood Serum and Cerebrospinal Fluid and the Nondiffusible Calcium in Sixty-Eight Normal Persons and in One Hundred and Thirty-One Patients with a Variety of Pathologic Conditions*

Condition	Cases	Blood Calcium, Mg. per 100 Cc.	Diffusible Calcium	Nondiffusible Calcium	+ Diffusible Calcium*	− Diffusible Calcium*	+ Nondiffusible Calcium*	− Nondiffusible Calcium*
Normal	68	9.2 -11.0	4.5 -5.5	4.75-5.75				
Pulmonary tuberculosis	63	8.1 -13.8	4.0 -7.75	3.34-8.87	22	5	14	19
Asthma	25	7.0 -12.67	4.39-6.33	1.5 -7.5	16	1	2	18
Mucous colitis	3	9.84-11.0	5.62-6.00	4.22-5.00	3	0	0	2
Vasomotor rhinitis	2	10.55-10.7	5.75-6.10	4.45-5.00	1	0	0	1
Angioneurotic edema	1	8.2	5.5	2.7	0	0	0	1
Tabes	6	9.85-12.25	5.23-6.21	4.62-6.04	5	0	1	2
Paresis	5	9.87-13.16	5.21-5.98	4.59-7.21	4	0	2	2
Arteriosclerotic dementia	3	11.34-15.1	5.03-6.53	6.25-8.57	2	0	3	0
Dementia praecox	3	10.37-10.97	5.82-6.73	4.24-4.55	3	0	0	3
Alcoholic dementia	2	9.7 -10.72	5.95-6.63	3.67-4.77	2	0	0	1
Mania	1	11.40	5.85	5.61	1	0	0	0
Epilepsy	4	10.15-11.2	5.0 -6.0	4.15-6.0	1	0	0	1
Imbecility	2	9.25- 9.6	4.9 -5.3	3.95-4.7	0	0	0	2
Mental deficiency	2	10.3 -11.5	5.6 -5.8	4.7 -5.7	2	0	0	1
Pregnancy	6	7.8 -11.59	4.5 -5.25	3.1 -6.76	0	2	4	1
Vasomotor ataxia	1	9.6	5.56	4.04	1	0	0	1
Paroxysmal dyspnea	2	8.2 -11.0	3.8 -5.0	4.4 -6.0	0	1	1	1
Total (abnormal)	131	7.0 -15.1	3.8 -7.75	1.5 -8.87	63	9	27	56

* The last four columns represent the number of cases in each group with increased and decreased diffusible and nondiffusible calcium values.

the remainder of the serum calcium being nondiffusible. The method used for the determination of calcium was the Clark-Collip modification of the Kramer-Tisdall method for serum calcium.[15] The results are detailed in tables 1 and 2.

COMMENT

The figures in the normal group are remarkably constant. The values for spinal fluid calcium coincide with those previously reported

14. Updegraff, H.; Greenberg, D. M., and Clark, G. W.: A Study of the Distribution of the Diffusible and Nondiffusible Calcium in the Blood Sera of Normal Animals, J. Biol. Chem. **71**:87, 1926.

15. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

for human beings by Halverson and Bergeim [11] and Pincus and Kramer,[12] although they are slightly above the figures obtained by Updegraff, Greenberg and Clark [14] by ultrafiltration. However, the ratio of spinal fluid to serum calcium, averaging 50 per cent, is in agreement with their figures for percentages of diffusible calcium. In twenty-one determinations on seventeen different normal persons, the latter investigators found that the variation in nondiffusible calcium was twice as great as that in the diffusible fraction. In this study, the normal values are at variance with this observation, the variation in both fractions being practically identical. In the abnormal group, however, the variation in nondiffusible calcium was approximately twice as great

TABLE 2.—*The Ratio of Diffusible to Total Serum Calcium and to Nondiffusible Calcium*

Condition	Cases	Ratio D/T*	Increased D/T	Decreased D/T	Ratio D/ND†	Increased D/ND	Decreased D/ND
Normal	68	45-55	..	..	82-115	..	..
Pulmonary tuberculosis	63	35.7-62.5	13	11	56.7-152	16	11
Asthma	25	40.8-80.0	17	2	68.9-400	19	2
Mucous colitis	3	54.5-59.1	2	0	120-133	3	0
Vasomotor rhinitis	2	53.5-57.8	1	0	115-137	1	0
Angioneurotic edema	1	67.1	1	0	203.7	1	0
Tabes	6	50.5-55.6	1	0	102-115	1	0
Paresis	5	45.2-55.3	1	0	82.5-124	2	0
Arteriosclerotic dementia	3	43.2-48.9	2	0	76.1-95.6	0	2
Dementia praecox	3	56.1-61.3	3	0	127-158	3	0
Alcoholic dementia	2	55.5-68.3	2	0	124-215	2	0
Mania	1	51.0	0	0	104	0	0
Epilepsy	4	45.4-59.0	1	0	83.3-144	1	0
Imbecility	2	51.0-57.2	1	0	104-134	1	0
Mental deficiency	2	50.4-54.0	0	0	101-119	1	0
Pregnancy	6	40.9-60.2	1	4	69.2-151	1	2
Vasomotor ataxia	1	57.9	1	0	137	1	0
Paroxysmal dyspnea	2	45.4-46.3	0	0	83.3-86.3	0	0
Total (abnormal)	131	35.7-80.0	47	19	56.7-400	53	17

* Ratios expressed as percentage. D refers to diffusible calcium and T to total serum calcium.

† ND refers to nondiffusible calcium.

as in the diffusible. That this is not entirely due to a greater independent variability of the nondiffusible portion is evidenced by the fact that the total serum calcium variation appeared to be more directly proportional to that in diffusible than in nondiffusible calcium.

Changes in the calcium content of spinal fluid obviously may be due to alteration in one or both of two variable factors; namely, the diffusibility of the blood calcium, and the permeability of the cell membrane interposed between the blood stream and the subarachnoid system. Diseases of the brain, cord and meninges, particularly inflammatory and vascular disorders and conditions causing increased intracranial tension, tend to increase local permeability. This may be determined by the increased concentration in the spinal fluid of foreign substances such as dyes and bromides after their administration intravenously. It is also evidenced by the increased concentration of certain relatively poorly

diffusible constituents of the fluid, such as proteins and dextrose. The latter substance has been studied by many investigators. Crawford and I [16] found a condition of hyperglycorrhachia in various nervous and mental disorders. The decrease in spinal fluid sugar noted commonly in meningitis is due, not to decreased permeability but, in all probability, to the glycolytic action of the leukocytes or bacteria present in the fluid in these cases. Therefore, the spinal fluid calcium in the twenty-eight patients included in the group having nervous and psychiatric disorders in the present study cannot be accepted as representing a condition of calcium diffusibility existing throughout the tissues, but must be interpreted as being of purely local significance.

The maintenance of the life and activity of cells can be explained only on the basis of a physiologic variation in permeability of the cell membrane. Certain functional states, such as the contraction of muscle fibers, are known to be accompanied by increased permeability to electrolytes. Krogh and Harrop [17] have shown that there is a constant alteration in capillary permeability in response to the needs of the tissue, probably dependent on the local accumulation of carbon dioxide, lactic acid and other metabolic products. This fact is of importance in disease states. If a condition of general increased or decreased cellular permeability exists, the passage of various poorly diffusible substances should be correspondingly altered to some degree. Wells [18] expressed the belief that in nephritis a toxic effect is produced on all cells as well as capillaries, resulting in an increase in permeability. Petersen [19] found abnormal degrees of capillary permeability in various conditions, notably pulmonary tuberculosis. Manwaring,[20] as a result of his studies, concluded that increased cellular permeability will eventually be found to be the dominant fundamental factor in protein sensitization and anaphylaxis.

In the determination of diffusible calcium by artificial membrane methods, this factor of variable cellular permeability is entirely disregarded; while it is of importance to recognize any alteration in the distribution of calcium in the blood serum as indicated by its diffusibility through a membrane of constant permeability, it is perhaps more

16. Crawford, B. L., and Cantarow, A.: The Routine Examination of Cerebrospinal Fluid, Am. J. M. Sc. **171**:859, 1926.

17. Krogh, A., and Harrop, G. A.: Some Observations on Stasis and Edema, J. Physiol. **54**:125, 1920-1921.

18. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 387.

19. Petersen, W. F.: The Permeability of the Skin Capillaries in Various Clinical Conditions, Arch. Int. Med. **39**:19 (Jan.) 1927.

20. Manwaring, W. H.; Chilcote, R. C., and Hosepian, V. M.: Capillary Permeability in Anaphylaxis, J. A. M. A. **80**:303 (Feb. 3) 1923.

important to know how much calcium has passed through the living membrane of variable permeability. This is particularly true in view of the important rôle that calcium plays in the regulation of cellular permeability. The ratio of diffusible to nondiffusible, or more correctly, of diffused to nondiffused calcium, is an expression of the distribution of calcium between the capillaries and tissues. The data presented here appear to be significant, indicating as they do some disturbance of a balance which is constant under normal circumstances. Any attempt to interpret these observations clinically would be beyond the province of the present discussion. However, it seems noteworthy that of the 103 patients suffering with disturbances other than those affecting the brain, cord and meninges, in only fifteen was the ratio of diffused to nondiffused calcium below normal, while in forty-two it was above normal limits. Still more significant is the fact that in a group of disorders probably representing an identical aberration of cellular function, as in the atopic patients, the observations are remarkably constant. Of the thirty-one subjects in this group only two showed a diminished ratio of diffused to nondiffused calcium, while twenty-four showed a distinct increase.

THE EFFECT OF MECHANICAL CONSTRICTION OF THE HEPATIC VEINS

WITH SPECIAL REFERENCE TO THE COAGULATION OF BLOOD *

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In 1925, in the laboratory of the department of pathology of the Northwestern University Medical School, a method was devised for blocking the outflow of blood from the liver by mechanical constriction of the hepatic veins in the dog.[1] This procedure permits a temporary exclusion of the liver and splanchnic area from the general circulation and their return to it at will, and makes possible a study of some of the functions of the liver. It has advantages over the more drastic methods formerly employed of removing the liver entirely,[2] or permanently shutting it out of the circulation by an Eck fistula.[3] The trauma produced by mechanical constriction of the hepatic veins is less severe. It is, however, an acute experiment. It must be done under a general anesthetic, and observations must be made at short intervals during constriction, lasting from ten to forty-five minutes—that is, before the effects of trauma wear off entirely. In the experiment with an Eck fistula, the animal can be allowed to recover from trauma and the anesthetic can be dispensed with. In this procedure, however, the liver cannot be returned to the circulation; neither can this be done with complete removal. Furthermore, with the Eck fistula there is always a possibility of a partial or complete reestablishment of the circulation in the liver. The method of mechanically constricting the hepatic veins therefore merits consideration on the grounds that it is less severe and permits the study of the early changes that occur when the liver is removed from the circulation and those following the return to the circulation of the liver after temporary removal by the constriction.

METHOD

The method of constricting the hepatic veins consists of making a midline abdominal incision about 4 inches (10.16 cm.) in length.

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* From the Department of Pathology, Northwestern University Medical School.

1. Simonds, J. P., and Brandes, W. W.: Effect of Obstruction of the Hepatic Veins on the Systemic Circulation, J. Physiol. **72**:320, 1925; Anaphylactic Shock and Mechanical Obstruction of the Hepatic Veins in the Dog, J. Immunol. **13**:1, 1927.

2. Mann, F. C.: Studies in the Physiology of the Liver: Technic and General Effects of Removal, Am. J. M. Sc. **161**:37, 1921.

3. Schäfer, E. A.: Textbook of Physiology, Edinburgh, J. Pentland Young, 1898, vol. 1, p. 908. Stern, H.: Beiträge zur Pathologie der Leber und des Icterus, Arch. f. exper. Path. u. Pharmakol. **19**:39, 1885.

Through this incision one end of a small-calibered rubber tube is passed through the foramen of Winslow. The two ends are then passed between the lobes of the liver and the parietal wall and diaphragm, over the ventral and anterior surface to the median fissure. To place the rubber tube in close proximity to the hepatic veins, it is passed through perforations made in the triangular ligaments when this can be done without hemorrhage. The two ends of the rubber tube are finally passed through two holes bored closely together in a small wooden block. To constrict the hepatic veins, traction is applied to the two ends of the rubber tube while, at the same time, the wooden block is pushed downward, the dog being in the supine position. The use of the block permits a more complete constriction of the hepatic veins and prevents great displacement or kinking of the inferior vena cava which would hinder the return circulation in that vessel.

EFFECT OF CONSTRICTION OF THE HEPATIC VEINS

The anatomic relationship of the hepatic veins varies somewhat in different animals. In some they are very short, emptying almost immediately into the inferior vena cava which makes complete constriction difficult without kinking the vena cava. In others they are longer and closely approximated, which is desired. In some dogs the ligaments extend to the free edge of the lobes of the liver and are narrow. This makes it difficult to perforate them without hemorrhage. Generally speaking, it was found that long, lean dogs that had been starved for twelve hours were best suited for this experiment.

All the experiments reported were performed with the animal under complete anesthesia. Ether was the anesthetic of choice because it gave greater relaxation.

Briefly stated, the changes [4] observed in the blood following constriction of the hepatic veins by the foregoing method for varying periods from ten to thirty minutes and the release of the constriction are as follows:

Blood Pressure.—There is a precipitate fall in blood pressure (carotid artery) of from 40 to 60 mm. of mercury. The pressure quickly reaches its lowest level and remains reasonably constant as long as the constriction is maintained. On release of the constriction the pressure rises to a level usually from 10 to 20 mm. of mercury above its initial value. This occurs in from about ten to fifteen seconds. The rise is followed shortly by a decrease of about 20 mm., after which the pressure rises slightly and maintains a constant level at or

4. Simonds, J. P., and Brandes, W. W.: Changes in the Blood Resulting from Mechanical Obstruction of the Hepatic Veins in the Dog, Am. J. Physiol. **86**:623, 1928.

near the value of that before constriction. Table 1 shows the average of the results from six dogs.

Simultaneously with the fall in arterial pressure that in the portal vein rises quickly to about twice the original value, and falls precipitately when the obstruction is released and the arterial pressure rises.

The percentage of fall in arterial pressure ranged from 26 to 42. It is not always possible to state that the obstruction to the hepatic veins is complete. In the dogs in which the fall ranged from 37.5 to 42 per cent, further traction on the rubber tube failed to reduce the blood pressure to any greater extent. It may be assumed, then, that complete obstruction to the hepatic veins will reduce the systemic blood pressure about 40 per cent. This does not mean that complete obstruction of the hepatic veins will reduce the total volume of circulating blood only 40 per cent. With the reduction in volume there is a compensatory vasoconstriction. This is shown by the fact that during

TABLE 1.—*Changes in Blood Pressure Resulting from Constriction*

Time of Observation	Blood Pressure, Mm. Hg.
Before constriction	125
2 minutes after constriction	70
5 minutes after constriction	68
10 minutes after constriction	68
15 minutes after constriction	69
1 minute after release	140
5 minutes after release	130
10 minutes after release	125
15 minutes after release	125

occlusion of the hepatic veins, epinephrine injected intravenously is virtually without effect because the peripheral blood vessels are already constricted.

The volume of the blood reaching the heart is one of the most important factors influencing blood pressure. The marked fall in blood pressure during constriction of the hepatic veins is due to the reduction in the volume of blood reaching the heart. The blood in the liver and splanchnic areas is prevented from returning to the heart. Burton-Opitz [5] estimated that the equivalent of the total quantity of blood in the body passed through the liver every three minutes. At any given moment there is a comparatively large volume of blood in this region which is greatly increased when the hepatic veins are constricted, since blood can still be forced into this area. Impounding such a large volume of blood and preventing it from returning to the heart is the cause of the low arterial blood pressure.

5. Burton-Opitz, R.: The Vascularity of the Liver, Quart. J. Exper. Physiol. **3**:300, 1910.

That a compensatory vasoconstriction occurs in consequence of hemorrhage has been shown.[6] In these experiments a vasoconstriction is also produced.[7] The sharp rise in blood pressure after release of the hepatic veins is probably not due alone to the delivery of a greater volume of blood to the heart, but also to the fact that the heart now delivers a larger volume into a greatly reduced or constricted vascular bed.

Blood Concentration.—With the method of Lamson and Roca,[8] it was found that in most dogs there was a rapid decrease in the concentration of the blood during the first five minutes of constriction of the hepatic veins. This was followed by a gradual recovery during the remainder of the period of constriction. The method used is based on determinations of the percentage of hemoglobin, the sample of blood taken before constriction being used as the standard and its value

TABLE 2.—*Changes in the Concentration of the Blood Resulting from Constriction*

Time of Observation	Blood Concentration per Cent
Before constriction	100.0
5 minutes after constriction	89.0
10 minutes after constriction	95.0
15 minutes after constriction	98.0
5 minutes after release	99.9
10 minutes after release	97.0
15 minutes after release	97.0
5 minutes after reconstriction	89.0
10 minutes after reconstriction	93.0
15 minutes after reconstriction	93.0
5 minutes after release	98.0

arbitrarily designated as 100. Although not free from criticism the method was considered sufficiently accurate to obtain comparative results in these experiments. The average of results in six dogs at corresponding intervals of time is shown in table 2.

The data in table 2 indicate that the blood becomes diluted rather quickly after mechanical constriction of the hepatic veins and then gradually increases in concentration. The increase in the outflow of lymph from the thoracic duct is a probable factor in the dilution of the blood. Fluid may enter from the tissues, as in low blood pressure, from hemorrhage, tending to restore the volume of blood.[9] These two sources of fluid may account for the dilution of the blood during the first five or ten minutes after constriction. The explanation for the gradual increase in concentration, while the constriction is still

6. Gesell, R.: Studies on the Submaxillary Gland: IV. A Comparison of the Effects of Hemorrhage and Tissue Abuse in Relation to Secondary Shock, Am. J. Physiol. **47**:502, 1919.

7. Simonds and Brandes (footnote 1, first reference).

8. Lamson, P. D., and Roca, J.: The Liver as a Blood Concentration Organ, J. Pharmacol. & Exper. Therap. **17**:481, 1921.

9. Guthrie, C. C.: Observations in Shock, Am. J. Physiol. **45**:544, 1918.

applied, is not so simple. Three possible sources of red cells may be concerned: 1. After the first few minutes of constriction, the fluid from the thoracic duct contains some red blood cells. 2. A general vasoconstriction may force more cells into the circulating blood stream. 3. The increased pressure in the liver may force the constriction and deliver into the circulation a small amount of blood highly concentrated by loss of fluid which has escaped from the liver through the thoracic duct.

Changes in the Liver.—With mechanical constriction of the hepatic veins there is a marked increase in the size of the liver. Its capsule becomes tense and its color much darker. Cut surfaces are very bloody. When the constriction is released and the blood pressure rises, there is a diminution in the size of the liver. Its capsule becomes less tense and the color less dark. These changes occur more slowly than do those following constriction.

TABLE 3.—*Changes in the Volume of Blood Sugar Resulting from Constriction*

Time of Observation	Dextrose, Mg. per 100 Cc. of Blood
Before constriction	128
5 minutes after constriction	109
10 minutes after constriction	101
15 minutes after constriction	74
5 minutes after release	157
10 minutes after release	173
15 minutes after release	168
5 minutes after reconstriction	167
10 minutes after reconstriction	143
5 minutes after release	147
10 minutes after release	157

The Flow of Lymph from the Thoracic Duct.—The flow of lymph from the thoracic duct, while the hepatic veins are constricted, shows an increase. The average increase in the number of drops for a series of six dogs was 5.2 times the number that escaped before and after constriction.[10] When the constriction is released there is a sharp decrease in the flow of lymph.

Blood Sugar.—A surprisingly rapid fall in blood sugar follows constriction of the hepatic veins (method of Folin and Wu).[11] Table 3 shows the average of results in six dogs.

As soon as the constriction of the hepatic veins is released, the blood sugar promptly rises to a level considerably higher than that before the veins were mechanically constricted. In one animal it rose to 435 mg. per hundred cubic centimeters of blood, the original level

10. Simonds, J. P., and Brandes, W. W.: The Effect of Mechanical Obstruction of the Hepatic Veins upon the Outflow of Lymph from the Thoracic Duct, J. Immunol. **13**:11, 1927.

11. Folin, O., and Wu, H.: A Simplified and Improved Method for the Determination of Sugar, J. Biol. Chem. **41**:367, 1920.

having been 163 mg. There was a slightly greater average fall in blood sugar in the first ten minutes following the first constriction (28 per cent) than in a similar interval after reconstriction (15 per cent). The average maximum fall in fifteen minutes after constriction was 42 per cent. This is considerably more than can be accounted for by dilution of the blood. Although it is not evident in table 3, the blood sugar not infrequently reaches a higher level after the second constriction than after the first.

The liver has been regarded as the organ that controls the blood sugar level, ever since Claude Bernard [12] found that blood from the hepatic veins constantly contained slightly more sugar than that in the portal vein, except during absorption of food. In 1857, he discovered glycogen and concluded that it was the chief source of carbohydrate material in the body. From it comes the dextrose of the blood. This theory was early upheld by Seegen [13] and most strenuously objected to by Pavy.[14] Later it was shown that removal of the liver or the shutting off of its blood supply in dogs [15] and in geese [16] was followed by either the disappearance or the marked diminution of the sugar of the blood. Recently it was shown that removal of the liver is followed by a progressive decrease in blood sugar with which symptoms develop that can be relieved by the administration of dextrose.[17] Hyperglycemia occurs after damage to the liver from poisoning with chloroform, hydrazine and phosphorus. The initial effect of these agents is a hyperglycemia.[18] Peptone injected intravenously produces changes in the blood sugar and gross changes in the liver strikingly similar to those obtained with mechanical constriction of the hepatic veins.[19] Ether anesthesia causes a slow, gradual rise in blood sugar.[20]

12. Bernard, Claude: Novelle function, du foil, Compt. rend. Acad. d. sc. **27**: 249, 253 and 514, 1848.

13. Seegen, J.: Die Zuckerbildung im Thierkörper, Arch. f. d. ges. Physiol. **50**:1, 1891; ibid. **51**:396, 1891.

14. Pavy, F. W.: The Physiology of Carbohydrates, London, J. & A. Churchill, 1894.

15. Tangl, F., and Vaughan, H.: Beitrage zur Physiologie des Blutzuckers, Arch. f. d. ges. Physiol. **61**:551, 1895. Schäfer (footnote 3, p. 921).

16. Minkowski, O.: Ueber die Folgen partieller Pankreasextirpation, Arch. f. exper. Path. u. Pharmakol. **31**:85, 1893.

17. Mann, F. C., and Magath, T. B.: Blood Sugar Decrease Following Hepatectomy, Arch. Int. Med. **30**:171 (July) 1922.

18. Bodansky, M.: The Production of Hypoglycemia in Experimental Derangements of the Liver, Am. J. Physiol. **66**:375, 1923.

19. Brandes, W. W., and Simonds, J. P.: Changes in the Blood Sugar Following the Injections of Peptone in the Dog, Am. J. Physiol. **86**:618, 1928.

20. Epstein, A. A., and Aschner, P. W.: The Effect of Surgical Procedures on the Blood Sugar Content, J. Biol. Chem. **25**:151, 1917. Epstein, A. A.; Reiss, J., and Branower, J.: The Effect of Surgical Procedures on Blood Sugar and Renal Permeability, ibid. **26**:25, 1918.

Stimulation of a sensory nerve, interference with hepatic circulation or the administration of certain drugs results in hyperglycemia.[21]

All the foregoing facts indicate that one of the early effects of stimulation or irritation of the liver is to cause its glycogen to be changed into dextrose, which is liberated into the blood stream. Obstruction of the hepatic veins causes a marked stasis in the liver, as evidenced by its gross changes. With this there is a local asphyxia and acidosis. Under the influence of these conditions, the glycogen present is changed into dextrose and the sugar of the blood in the liver becomes highly concentrated. The sugar in the general circulation is used up in metabolism and is not replaced as long as the blood from the liver is prevented from entering the general circulation. This will explain the decrease in blood sugar while the liver is shut out of the general circulation, and the marked increase after release, since the blood coming from the liver now is highly concentrated with dextrose. The agency converting glycogen into dextrose is believed to be the diastatic enzyme, glycogenase, which is present not only in the liver cell but also in the blood and lymph. That glycogen can exist in the liver cells in the presence of this powerful enzyme must be explained by the theory that its activities are held in check by inhibiting influences, which are under nervous or hormone control.[22] The action of glycogenase is extremely susceptbile to changes in p^H for it has been shown that an increase in the hydrogen ion concentration of the blood flowing to the liver cells excites glycogenolysis.[23] That this, however, is the only factor in the process has been questioned.[24]

Changes in the hydrogen ion concentration are commonly observed in conditions in which there is also an increase in blood sugar. In severe hemorrhage a measurable increase in acidosis has been reported,[25] and hemorrhage increases the blood sugar.[26] Carbon monoxide given subcutaneously causes marked hyperglycemia,[27] and sodium bicarbonate, sodium carbonate and other alkalis have an inhibitory influence on the

21. Brunings, W.: Ein neuer Apparat für Blutorperchonzahlung, Arch. f. d. ges. Physiol. **96**:308, 1903.

22. Macleod, J. J. R., and others: Physiology and Biochemistry in Modern Medicine, ed. 5, St. Louis, C. V. Mosby Company, 1926, p. 888.

23. Langfeldt, E.: Blood Sugar Regulation and Origin of Hyperglycemia, J. Biol. Chem. **46**:381 and 391, 1921.

24. Tatum, A. L.: Alkaline Reserve Capacity of Whole Blood and Carbohydrate Mobilization as Affected by Hemorrhages, J. Biol. Chem. **41**:59, 1920.

25. Crile, G. W.: Studies in Exhaustion: V. Hemorrhage, Arch. Surg. **7**: 154 (July) 1923.

26. Mulinos, M. G.: Hemorrhage Hyperglycemia, Am. J. Physiol. **86**:70, 1928.

27. Mikamu, Shago: Simultaneous Determinations of Blood Sugar Content and the Gas Content and Alkalinity of the Arterial Blood During Carbon Monoxide Poisoning, Tohoku J. Exper. Med. **8**:237, 1926-1927.

hyperglycemia of rabbits poisoned with carbon monoxide.[28] In the hyperglycemia accompanying ether anesthesia there is also an increase in hydrogen ion concentration. This increase is supposed to be dependent to a large extent on the production of lactic acid.[29]

In the foregoing experiments colorimetric determinations of the p^H were made on the plasma. The samples of blood were collected, under oil, from the jugular vein. In all dogs there was a definite decrease in the p^H, ranging from 0.1 to 0.3, an average decrease of 0.2. The greatest changes were apparent after the constriction of the hepatic veins was released. There was also a change in the hydrogen ion concentration associated with hyperglycemia.

Coagulation Time of the Blood.—During constriction of the hepatic veins the coagulation time of the blood was definitely decreased. This was shown by Sabraze's capillary tube and Biffe's wire loop methods. In the former, blood is drawn into capillary tubes; small portions are broken off at regular intervals until a strand of fibrin stretches across the gap. This is taken as the end point. In the latter method the wire loops are loaded with a film of blood; the loops are lowered into distilled water (38 C.) at regular intervals. When the blood does not diffuse out but remains solid in the loop, coagulation has taken place.

With both these methods the normal coagulation time in these dogs varied between two minutes and thirty seconds, and four minutes and twenty seconds. With such a short time for the normal, changes brought on by various procedures do not stand out so plainly. The two methods gave favorable checks for comparative results in these experiments. The average results in a series of dogs appear in table 4.

In order to avoid the difficulties mentioned, the method of Hayem was employed in another series of experiments. The jugular vein was exposed and covered with petrolatum. Two cubic centimeters of blood was drawn from this vein into a syringe treated with petrolatum. The blood was slowly run into a test tube ⅜ by 3 inches (0.9 by 7.6 cm.). This was placed in a water bath at 38 C. The tube was tilted every fifteen or thirty seconds until it could be inverted without spilling the contents. This was taken as the end-point. With this method, several points in technic[30] were carefully observed: (*a*) The temperature was kept constant; (*b*) the method of obtaining the samples was uniform; (*c*) the amount of foreign contact was the same in each sample, and

28. McDonell, L., and Underhill, F. P.: Studies on Carbohydrate Metabolism: XIV. Influence of Alkali Administration upon Blood Sugar Content in Relation to the Acid-Base Producing Properties of the Diet, J. Biol. Chem. **29**:227, 1917.

29. Ronzoni, E.; Koechig, I., and Eaton, E. P.: Rôle of Lactic Acid in the Acidosis of Ether Anesthesia, J. Biol. Chem. **61**:465, 1924.

30. Addis, T.: The Coagulation of Blood (Time) in Man, Quart. J. Exper. Physiol. **1**:305, 1908.

(*d*) the end-point was sharp and indicated approximately the same degree of coagulation. Special care was taken to avoid injury to the tissues when the sample was drawn in order to prevent the admixture of tissue juice with the drawn blood. The average results obtained with this method are shown in table 5.

The percentage of error in Hayem's method, as applied in these experiments, was determined to be about 10.

From table 5 it is evident that there is a decrease in the coagulation time of the blood within fifteen minutes after constriction of the hepatic veins. With the first methods this was about 50 per cent; with the latter about 25.4 per cent.

TABLE 4.—*Changes in Coagulation Time Resulting from Constriction, Tested by Sabraze's Capillary Tube and Biffe's Wire Methods*

Time of Observation	Coagulation Time, Seconds
Before constriction	206
5 minutes after constriction	127
10 minutes after constriction	93
15 minutes after constriction	93
5 minutes after release	139
10 minutes after release	149
15 minutes after release	159
5 minutes after reconstriction	103
10 minutes after reconstriction	91
5 minutes after release	135

TABLE 5.—*Changes in Coagulation Time, According to Method of Hayem*

Time of Observation	Coagulation Time	
	Minutes	Seconds
Before constriction	12	40
5 minutes after constriction	11	20
10 minutes after constriction	10	30
15 minutes after constriction	9	15
5 minutes after release	10	50
10 minutes after release	12	10
15 minutes after release	13	0

An effort was made to determine what other changes might have occurred in the blood following constriction of the hepatic veins to account for this decrease in the coagulation time.

Blood Fibrin: Determinations of blood fibrinogen were made according to the gravimetric method of Foster and Whipple.[31] The fibrin was precipitated by recalcifying oxalated plasma. It was found that 1 cc. of a 1 per cent solution of sodium oxalate did not prevent coagulation of all the samples drawn after the hepatic veins had been constricted. One cubic centimeter of a 2 per cent solution was then used as the anticoagu-

31. Foster, D. P., and Whipple, G. H.: An Accurate Method for the Quantitative Analysis of Blood Fibrin in Small Amounts, Am. J. Physiol. **22**:58, 1921.

lant. The fibrin values, expressed in milligrams per hundred cubic centimeters of blood, were calculated by Gram's formula: [32]

Total oxalated blood—total volume cells fibrin in 2 cc. oxalated plasma, 100.—Total oxalated blood—volume oxalate solution × 2 equals milligrams of fibrin in 100 cc. of blood. The average of results obtained in a series of six dogs is shown in table 6.

There is a decrease of slightly over 10 per cent in fibrinogen after the hepatic veins are constricted. The decrease is no greater than what can be accounted for by dilution of the blood. The release after constriction of fifteen minutes or more is followed by a definite increase (21 per cent) in fibrinogen value.

Various organs have been considered as the site of the formation of fibrinogen. Brown-Séquard,[33] Dastre,[34] Matthews [35] and others concluded that it was formed in the intestines. Doyon and Gautier [36] decided that the intestines, while not essential to its production, contributed to its formation. The lungs and skin [34] have been considered as its seat of origin. The decreased coagulability of the blood in phosphorus [37] and chloroform [38] poisoning has been shown to be due to the disappearance of

TABLE 6.—*Determinations of Blood Fibrinogen Before and After Constriction*

Time of Observation	Mg., per 100 Cc.
Before constriction	280
10 to 15 minutes after constriction	250
5 minutes after constriction	340

fibrinogen. In animals with an Eck fistula the fibrinogen in the blood was found to disappear rapidly and there was no regeneration.[39] Total

32. Gram, H. C.: A New Method for the Determination of Fibrin Percentage in Blood and Plasma, J. Biol. Chem. **49**:279, 1921.

33. Brown-Séquard, E.: Sur des faits que semblent montrer que plusieurs kilogrammes de fibrine se forment et se transforment, chaque jour, dans le corps de l'homme, et sur le siège de cette production et de cette transformation, J. de physiol. et de path. gén. **1**:298, 1858.

34. Dastre, A.: Contribution a l'étude de l'évolution du fibrinogène dans le sang, Arch. de Physiol. **5**:327, 1893.

35. Matthews, A.: The Origin of Fibrinogen, Am. J. Physiol. **3**:53, 1899.

36. Doyon, M., and Gautier, C.: Sur le rôle de l'intestine dans la fibrinogénèse, J. de physiol. et de path. gén. **9**:405, 1907.

37. Corin, G., and Ansiaux, G.: Untersuchungen über Phosphorvergiftung, Vrtljschr. f. gerichtl. Med. **7**:80, 1894. Jacoby, M.: Ueber die Beziehungen der Leber und Blutveranderungen bei Phosphorvergiftung zur Autolyze, Ztschr. f. Physiol. Chem. **30**:174, 1906.

38. Doyon, M.: Incoagulabilité du sang provoquée par le chloroform; rôle du foie, Compt. rend. Soc. de biol. **58**:30, 1905. Whipple, G. H., and Hurwitz, S. H.: Fibrinogen of the Blood as Influenced by Liver Necrosis of Chloroform Poisoning, J. Exper. Med. **8**:136, 1911.

39. Meek, W. J.: Relation of the Liver to the Fibrinogen Content of the Blood, Am. J. Physiol. **30**:161, 1912.

removal of the liver causes a progressive decrease in fibrinogen.[40] Diseases of the liver in which there is destruction of parenchyma are associated with decrease in fibrogen.[41] The evidence from the literature that fibrinogen is formed solely in the liver is, thus, quite convincing. In the present experiments performed the increase in fibrinogen after release of the hepatic veins can be assumed to be due to a stimulation of the liver by the stasis, to increased formation of fibrinogen, or to the accumulation in the hepatic blood of fibrinogen formed at a normal rate. In either case an excess is set free in the blood after the constriction is released. The decrease during constriction was slight and can be explained on the basis of dilution alone. The change in coagulation time cannot be satisfactorily explained on the basis of the fibrinogen factor, at least not on the changes in quantity of this element.

The theory has been advanced that blood proteins constitute merely a continuous series of disintegration products of tissue proteins, of which the first step is the least dispersed of the blood proteins, fibrinogen.[42] This theory accounts well for the increase in fibrinogen content with injury to the tissues. Applying it to the foregoing observations, one would expect a heightened coagulability of the blood when blood which had stagnated in the liver and splanchnic regions was returned to the circulation.

Blood Platelets: Blood platelet counts were made before and after constriction and release of the hepatic veins, by the method of Spitz.[43]

The averages of results are given in table 7.

The platelets during constriction of the hepatic veins show a decrease of about 24 per cent. A decrease in these elements would be expected as a result of dilution of blood following the sudden withdrawal of such a large volume of blood from the general circulation. The table shows but a slight increase in number of platelets after release of the constriction. If the blood impounded in the liver contained the normal number of these elements, a greater rise, perhaps, might be expected after releasing this blood. Many of the platelets in this area probably disintegrate during the period of constriction as a result of stasis. Changes in the p^H may also be factors in their disintegration.

It is as yet unsettled just what part the platelets play in the process of coagulation. In thrombosis it has often been observed that fibrin is

40. McMaster, P. D., and Drury, D. R.: The Source of Fibrinogen, Proc. Soc. Exper. Biol. & Med. **26**:490, 1929.

41. Isaac-Krieger, K., and Hiege, A.: Der Fibrinogengehalt des Blutes bei Leberkrankungen, Klin. Wchnschr. **2**:1067, 1923.

42. Hertzfield and Klinger: Biochem. Ztschr. **83**:43, 1917, cited by Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 350. Starlinger, W., and Frisch, A.: Chemisch-Physikalische Blutuntersuchungen zur Frage der Protoplasmaaktioaung, Ztschr. f. d. ges. exper. Med. **24**:143, 1921.

43. Thomsen, O., cited by Reiman, H. A.: The Blood Platelets in Pneumococcus Infection, J. Exper. Med. **40**:553, 1924.

first formed about masses of platelets clinging to the wall of the vessel. This indicates that they take part in the process. Howell [44] and others stated their belief that they give rise to thromboplastic substances, cephalin which neutralizes antithrombin. They are considered more important than the leukocytes in producing substances that participate in the coagulating mechanism.[45] It is also stated that platelet counts below 100,000 in the human being are generally accompanied by a tendency to bleed.[46] Tait and Green [47] stated that the thrombocytes of the frog are essential to the initiation of the clotting mechanism. Tait and Burke [48] observed that deplateletized mammalian blood does not clot on contact with foreign matter. They concluded that platelets are essential to the process. Mills [49] showed that platelets contain tissue fibrinogen.

The results of the experiments reported do not give definite evidence of the rôle of platelets in the process of coagulation. There is a decrease in number during constriction of the hepatic veins that is also associated with a decrease in coagulation time. This decrease in platelets, however, is not marked, and there is no evidence that it is due to disintegration of

TABLE 7.—*Blood Platelet Counts Before and After Constriction of the Hepatic Veins*

Time of Observation	Platelets per Cu. Mm.
Before constriction	292,800
10 to 15 minutes after constriction	220,320
10 to 15 minutes after release	235,400

platelets in the general circulation. It seems more probable that it is due to marked changes in the volume of blood.

It was frequently noted that the coagulation time taken immediately after release of the constriction of the hepatic veins was noticeably shortened beyond what it was during constriction. The platelets increased only slightly on release. It may be assumed that platelets disintegrated in the area of blood stasis. After release of the constriction there is also an increase in fibrin. These factors would tend to increase the

44. Howell, W. H.: Textbook of Physiology, ed. 10, Philadelphia, W. B. Saunders Company, 1927, p. 468.

45. Bordet, J., and Delange, L.: La coagulation du sang et la génèse de la thrombine, Ann. de l'inst. Pasteur **26**:657, 1912; Bull. Johns Hopkins Hosp. **32**: 213, 1921.

46. Gram, H. C.: On the Platelet Count and Bleeding Time in Diseases of the Blood, Arch. Int. Med. **25**:325 (March) 1920.

47. Tait, J., and Green, F.: The Spindle Cell in Relation to Coagulation of the Frog's Blood, Quart. J. Exper. Physiol. **16**:141, 1926.

48. Tait, J., and Burke, H. E.: Platelets and Blood Coagulation, Quart. J. Exper. Physiol. **16**:129, 1926.

49. Mills, C. A.: The Rôle of the Platelets on Blood Clotting, Chinese J. Physiol. **1**:235, 1925.

coagulability. This tendency is shortly replaced by prolongation of the coagulation time.

Blood Calcium: Ionized calcium (Sabbatini) is essential to coagulation, since blood from which calcium has been precipitated does not clot. The mechanism of its action has not been agreed on. Pekelharing, Harmmarsten and Morawitz [50] thought it necessary for the transformation of prothrombin into thrombin. Howell [51] expressed the belief that calcium activates prothrombin whenever it is not inhibited by antithrombin.

In the foregoing experiments, the method of Kramer and Tisdall [52] being used for the determination of blood calcium, the results were as given in table 8.

These results show that there is a decrease of about 15 per cent in the calcium of the blood during constriction. This parallels the change in the concentration of the blood and can be explained on a basis of dilution of the blood. Hence, changes in this factor can hardly be considered sufficient to account for the changes in coagulability of the blood.

TABLE 8.—*Determinations of Blood Calcium Before and After Constriction*

Time of Observation	Mg., per 100 Cc. of Blood
Before constriction	10.5
10 to 15 minutes after constriction	8.8
10 to 15 minutes after release	9.0

In order to determine the effect of dilution on the coagulation time, 0.85 per cent sodium chloride solution was injected intravenously in quantities sufficient to dilute the blood from 10 to 30 per cent. Before injection the coagulation time averaged eleven minutes and ten seconds; from five to ten minutes after, it averaged ten minutes and fifty seconds. Mere dilution, therefore, causes practically no change in the coagulation time. In animals that were first bled from 50 to 100 cc. and then were given an injection of an equal volume of physiologic solution of sodium chloride there was a decrease in coagulation time of 26 per cent within ten minutes. By this procedure a marked dilution of the blood was produced, but there was also the added feature of hemorrhage.

Clamping of the inferior vena cava above the entrance of the level of the renal veins caused practically no change in coagulation time during the first five minutes. After ten minutes a slight decrease, an average of 11 per cent, was noted. This decrease is small and can be considered

50. Pekelharing, Harmmarsten and Morawitz, cited by Wells: Chemical Pathology, p. 352.

51. Howell (footnote 44, p. 466).

52. Kramer, B., and Tisdall, F. F.: Method of Determining Blood Calcium, J. Biol. Chem. **47**:475, 1921; ibid. **48**:233, 1921.

within the range of experimental error. Clamping of the inferior vena cava at the aforesaid level removes a large volume of blood from the circulation. While this does not equal the volume withheld when the hepatic veins are occluded, these experiments indicate that the mere removal of a volume of blood from the circulation is not the only factor in decreasing the coagulation time under the conditions of these experiments.

In a limited number of animals the p_H of the blood from the jugular vein was determined. In each case there was a definite decrease. Further work, however, is being carried out on this and on the carbon dioxide, prothrombin and antithrombin factors.[53]

COMMENT

Several factors suggest themselves as possibly concerned in the definite decrease in coagulation time during mechanical constriction of the hepatic veins:

1. The effect of trauma may be considered. It is believed by some writers that trauma in itself does not affect the coagulation time.[53] In the experiments cited, this was shown not to be the only factor, in the following way: The animals were anesthetized and, after all operative trauma had been committed, the coagulation time was allowed to become stabilized during the following thirty or sixty minutes. Constriction of the hepatic veins at this time caused a definite decrease in coagulation time. It is evident, therefore, that constriction alone causes a change.

2. Coagulation time is gradually shortened during ether anesthesia.[53] This is said to occur within the first fifteen minutes after induction and is believed to be the result of an outpouring of epinephrine.[54] The liver is regarded as essential to the action of epinephrine in increasing coagulability of the blood. It is stimulated by this agent to increased production of prothrombin.[55] A possible excess of epinephrine will not explain the decreased coagulation time in these experiments because the liver was excluded from the circulation. Hemorrhage has been reported to cause an increased output of epinephrine. After suprarenalectomy, however, hemorrhage will decrease the coagulation time,[56] and double adrenalec-

53. Rabinovich, M.: Coagulation Time of the Blood During Anesthesia, Brit. J. Exper. Path. **8**:343, 1927.

54. Cannon, W. B.: The Emergency Function of the Adrenal Medulla in Pain and the Major Emotions, Am. J. Physiol. **33**:357, 1913. Cannon, W. B., and Mendelhall, W. L.: Pain and Emotional Disturbances of Coagulation Time, Am. J. Physiol. **34**:251, 1914.

55. Grahfield, G. P.: Factors Affecting the Coagulation Time of the Blood: IX. The Effect of Adrenin on the Factors of Coagulation, Am. J. Physiol. **42**:46, 1917.

56. Hirochi, Tachi: Simultaneous Determinations of the Epinephrine Liberation and the Sugar Content and the Coagulation Time of the Blood in Non-Anesthetized, Non-Fasted Dogs After Hemorrhage, Tohoku J. Exper. Med. **11**:205, 1928.

tomy in cats has been found progressively to decrease the coagulation time.[57]

3. Changes in the concentration of blood sugar are frequently found associated with changes in the coagulation time of the blood. It has been thought that this might be a possible cause, indirectly, by stimulating the liver to the production of more fibrinogen.[58] Cannon, however, showed that injection of sugar alone has no effect on coagulation time. In the foregoing experiments also the decrease in coagulation time occurred during constriction when there was a definite hypoglycemia, and increased after release of constriction of the hepatic veins when the blood sugar level was at its highest point.

4. Changes in the concentration of the blood may cause changes in the coagulation time. When blood becomes more dilute the bodies concerned in coagulation are also diluted, which should cause an increase in coagulation time unless there is an excess of coagulating factors in the blood or unless dilution affects those bodies which inhibit coagulation more than it affects those which cause clotting. If this is the case a considerable degree of dilution may occur before there is a noticeable effect on coagulation, or dilution of anticoagulant factors may even shorten the coagulation time. The greatest dilution occurred shortly after the hepatic veins were constricted. The coagulation time became shorter at the same time or slightly later. It is possible that lymph from the thoracic duct, which is greatly increased during constriction, may carry coagulating factors to the blood. A definite impression was gained that lymph collected during the period of constriction clotted with greater rapidity and more firmly than that collected before constriction. Dilution of the blood, and, thus, of the factors concerned in coagulation by the intravenous injection of a volume of physiologic solution of sodium chloride equal to 30 per cent of the total volume of the blood, caused practically no change in coagulation time.

5. Conditions that cause changes in coagulation are also associated with changes in p^H. In ether anesthesia there is a definite decrease in p^H as well as a decrease of the coagulation time of the blood.[59] The carbon dioxide capacity of the plasma decreased 36.9 per cent in two hours of ether anesthesia.[60] The injection of a weak acid into dogs caused a

57. Barlow, O. W., and Ellis, M. M.: Effect of Double Adrenalectomy on the Coagulation Time in Cats, Am. J. Physiol. **70**:58, 1924.

58. Partoo, A., and Svee, F.: Gesetzmuziger zuzammenhang zwischen Blutzucker Gehalt und Blut, Deutsche med. Wchnschr. **53**:1857, 1927.

59. Van Slyke, D. D.; Austin, J. H., and Cullen, G. E.: The Effect of Ether Anesthesia on the Acid-Base Balance of the Blood, J. Biol. Chem. **53**:277, 1922.

60. Atkinson, H. V., and Ets, H. N.: Chemical Changes of the Blood Under the Influence of Drugs, J. Biol. Chem. **52**:5, 1922.

reduction of the alkali reserve to a low level. At the same time there was a shortening of coagulation time.[61] Injection of an alkaline solution of the same strength, after the acid had been injected, caused a rise in alkali reserve and a lengthening of the coagulation time. Fibrinogen, the precursor of fibrin which is the basic element of a blood clot, is present in the plasma as a dispersed colloid. In the process of clotting, fibrinogen (hydrosol) is changed into fibrin (hydrogol). Electromatric fibration has determined the iso-electric point of fibrin to be p^H 5.5.[62] The iso-electric point of blood, that is, the hydrogen ion concentration at which blood coagulates, is about p^H 4.6.[63] Clotting of rabbit's plasma has been found to be accompanied by a sudden but slight diminution of its alkalinity.[64]

In the experiments described there was a definite decrease in the p^H and alkali reserve during constriction of the hepatic veins. It is not known whether variations in p^H affect coagulating factors more than anticoagulating factors. In the foregoing experiments, however, the coagulation time increased after release of the hepatic veins, the period when the p^H was lowest. This suggests that possibly there was present in the blood an anticoagulant factor of hepatic origin either formed by the liver or produced as a result of possible injury to the liver. This would be in harmony with the theory of Howell.[65] There is no satisfactory method for a quantitative determination of heparin in the blood and, considering that it has proved to be a carbohydrate body and probably a glycuronic acid, there is little probability that a method of this kind can be devised.[66] It may be argued that antithrombin is present in the blood and in fifteen minutes' time does not change sufficiently to cause alterations in coagulation time. The anticoagulant action of heparin, however, has been shown to wear off rapidly in vitro [67] and when injected into dogs.[68]

61. Mills, C. A.: The Action of Tissue Extracts in the Coagulation of the Blood, J. Biol. Chem. **46**:167, 1920.

62. Nordbo, R.: Zur physikalischen Chemie des Fibrinogen, Biochem. Ztschr. **191**:150, 1927.

63. Alexander, J.: Colloid Chemistry, Theoretical and Applied, New York, Chemical Catalog Company, 1928, vol. 2, p. 425.

64. Hirsch, E. F.: Changes in Hydrogen Ion Concentration of the Blood with Coagulation, J. Biol. Chem. **61**:795, 1924.

65. Howell, W. H.: Two New Factors in Blood Coagulation: Heparin and Pro-Antithrombin, Am. J. Physiol. **47**:328, 1917; The Purification of Heparin and Its Presence in Blood, ibid. **71**:553, 1925.

66. Howell, W. H.: Personal communication to the author.

67. Gross, P.: Duration of Anticoagulant Action on Heparin in Vivo in Relation to Dosage, Proc. Soc. Exper. Biol. & Med. **26**:383, 1929.

68. Shionoya, Takuji: Studies in Experimental Extra-Corporeal Thrombosis: III. Effects of Certain Anticoagulants (Heparin and Hirudin) in Extracorporeal Thrombosis and on the Mechanism of Thrombus Formation, J. Exper. Med. **46**: 21, 1927.

In brief, the factors which seem to be most concerned in the changes in coagulation time in these experiments are as follows: (*a*) A disintegration of platelets occurs which would give rise to more tissue fibrinogen (Mills), cephalin (Howell) and thrombokinase (Morawitz). This factor would not explain the increase in coagulation time after release of the constriction. (*b*) Changes in the hydrogen ion concentration are in the direction of changes associated with conditions in which the coagulation time is decreased. (*c*) Changes take place in the anticoagulant element (heparin) which would explain both the decrease in coagulation time during constriction of the hepatic veins and the increase in coagulation time after release of the constriction.

SUMMARY

1. A method of mechanically constricting the hepatic veins in the dog has been described. This procedure permits a study of changes occurring in the blood following removal of the liver from, and its return to, the circulation.

2. Following this constriction there is a precipitate fall in blood pressure of from 40 to 60 mm. of mercury, a level which is then maintained reasonably constant for twenty minutes or more.

3. A decrease in the concentration of the blood (an average of 11 per cent in six dogs) with a gradual increase in concentration occur until, at the end of fifteen minutes, the normal value is approximately reached.

4. A rapid decrease in blood sugar (average of 42 per cent) is obtained during constriction for fifteen minutes with a rapid rise after release.

5. A definite decrease in coagulation time of from 25 to 50 per cent is observed during constriction, followed by an increase on release.

6. There was a slight decrease of fibrinogen (11 per cent) during constriction and a definite increase of 25 per cent or more on release of constriction.

7. The platelets were slightly decreased (15 per cent) during constriction with slight change on release.

8. Changes in blood calcium can be accounted for by dilution.

9. The experimental results reported indicate that the chief factors, the interaction of which is concerned in the changes in coagulation time during and after constriction of the hepatic veins, are: (*a*) alterations in antithrombin (heparin) content; (*b*) increase in the hydrogen ion concentration, and (*c*) numerical changes in platelets.

OPIUM ADDICTION

IX. WATER BALANCE STUDIES DURING THE ADMINISTRATION AND THE WITHDRAWAL OF MORPHINE *

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Abrupt withdrawal of morphine from human addicts is practically always associated with loss of weight during the manifestation of the so-called "withdrawal symptoms." During this period, the addicts invariably refuse to take any nourishment, their water intake is practically negligible and increased perspiration is noted. It is the object in this paper to report the results of our studies of water balance in five addicts, as well as in three normal persons, given the same diet, in order to determine whether the loss of weight is due entirely to inanition, or in part to an additional loss of water as the result of increased metabolism.

METHODS

Water balance was estimated by the method of difference of weight. The diet employed consisted of a modified Folin [1] diet prepared each morning, the ingredients used being: eggs, whole milk, cream, malted milk, coffee, vanilla, Welch's grape juice and sugar, as well as 7 Gm. of salt and 25 Gm. of candy, in addition to water. These substances were prepared in various combinations, and administered in the same quantities, at the same hour each day, throughout the experiment. The normal subjects, first-year medical students in the School of Medicine of the University of Pennsylvania, who were taking their final examinations in anatomy and chemistry, were able to continue this regimen throughout the seven days of the experiments. The addicts succeeded in retaining all food administered while they were receiving their drug. Only two, however, accepted and retained the food during the forty-eight hour withdrawal of morphine, and one of these refused the additional water that was included in the day's proffer of food and drink. In the table is given the number of calories administered per day together with the amounts of protein, carbohydrate and fat from which the caloric intake was calculated.[2]

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* From the Narcotic Wards of the Philadelphia General Hospital.

* The expenses of this research were defrayed by the Committee on Drug Addictions, New York City, and the studies were carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital, which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

1. Folin, Otto: Approximately Complete Analyses of Thirty Normal Urines, Am. J. Physiol. **13**:44, 1905.

2. Lusk, Graham: The Elements of the Science of Nutrition, Philadelphia, W. B. Saunders Company, 1923, p. 42.

The subjects were weighed exactly at 9 o'clock each morning, on a silk scale of the type proposed by Benedict and Root,[3] the scale weighing accurately to within 10 Gm. The subjects were required to remove all clothing following the weighing, the clothing then being weighed separately and deducted from the total weight obtained. Before being weighed, all subjects were required to pass their urine and defecate if possible. The last administration of a food mixture was given at 3 a. m., the last administration of water, at 6 a. m. Dietetic scales were used to measure to within a gram the amount of food and water taken.

All urine, feces, vomitus and blood were collected and weighed on a scale in the ward, with an accuracy of within 1 Gm. The total collections were again reweighed in the laboratory as a check on the amounts obtained in the ward. Toluene was used to preserve the urine.

The Kjehldahl method was used for the determination of the amount of nitrogen in the urine and dried feces. The amount of uric acid of the urine was determined by the method of Benedict and Franke.[4] The Folin colorimetric method[5] was used to determine the amount of creatinine of the urine. We are indebted to Austin and Sunderman[6] for the method of calculating the water balance.

Throughout this study we have made an arbitrary allowance for maximal error for each measurement and estimate. This allowance for error is designated in text and table by the symbol ± and must not be confused with probable error or other statistical function.

Calculation of Water Balance.

Measured intake (grams):

(1) $I = (\text{food} + \text{beverage} + \text{enema in grams}) \pm 2$ per cent.

Measured intake of water (grams):

(2) $W_i = (\text{water of food estimated from tables [but not the water of oxidation]} + \text{beverage} + \text{enema}) \pm 2$ per cent.

Water of oxidation of food intake (grams):

(3) $W_{ox.\ i} = (0.413\ P_i + 0.555\ C_i + 1.071\ F_i) \pm 2$ per cent in which P_i, C_i and F_i are the grams of protein, carbohydrate and fat in the intake. The amount of water formed by oxidation is taken from Magnus-Levy's calculations that 100 Gm. of protein give 41.3 Gm. of water, 100 Gm. of carbohydrate give 55.5 Gm. of water and 100 Gm. of fat give 107.1 Gm. of water.

Total water intake (grams):

(4) $W_{ti} = W_i + W_{ox.\ i}$.

Measured output (grams):

(5) $O = (\text{urine} + \text{feces} + \text{sputum} + \text{blood removed}) \pm 2$ per cent.

Measured water output (grams):

(6) $W_o = (W_u + W_{fec} + W_{sp} + W_{bl}) \pm 2$ per cent.

Daily change in weight (grams):

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3. Benedict, F. G., and Root, H. L.: Insensible Perspiration: I. Its Relation to Human Physiology and Pathology, Arch. Int. Med. **38**:1 (July) 1926.

4. Benedict, S. R., and Franke, Elizabeth: A Method for the Direct Determination of Uric Acid in Urine, J. Biol. Chem. **52**:387, 1922.

5. Folin, Otto: Beitrag zur Chemie der Kreatinins und Kreatins im Harne, Ztschr. f. phys. Chem. **41**:223, 1904.

6. Austin, J. H., and Sunderman, F. W.: Water Metabolism in Pneumonia, to be published.

(7) $\Delta Wt =$ (initial weight—final weight) $\pm$ 20 Gm. for the period. In the estimation of mean increment per day, this allowance for error is divided by the number of days in the period.

Weight loss through skin and lungs (grams):

(8) $-\Delta Wt_{s.l.} = -\Delta Wt - (O—I)$.

Weight loss due to excess of CO_2 in grams over O_2 in grams:

(9) $(CO_2 - O_2) = 75 \pm 75$.

This range is taken as sufficiently inclusive to cover any reasonable variation in total metabolism and respiratory quotient.

Water loss through skin and lungs, neglecting the solids of the sweat, which are assumed to be less than 0.5 per cent of the water loss (grams):

(10) $W_{s.l.} = (-\Delta Wt_{s.l.} - [CO_2 - O_2]) \pm$ error (table may be seen here).

Total water output (grams):

(11) $W_{t.o.} = (W_o + W_{s.l.}) \pm$ error (table).

Absolute daily water balance:

(12) $WBal_{abs.} = (W_{i.t.} - W_{t.o.}) \pm$ error (table).

RESULTS

Examination of the table giving the data relative to the water metabolism shows:

1. The three controls and all the addicts, except addict 3, were in water balance within our allowance for error in their first periods, while receiving the drug. Addict 3 in the first period, while receiving the drug, suffered a water loss.

2. During the two or three days of withdrawal of morphine, a definite and usually great negative water balance occurred. This occurred in two subjects, addicts 1 and 2, without diminution in the intake of food, although in the latter diminution in fluid intake accounted for half of the loss. Both, however, showed increased water output. In the other three subjects, the diminished intake of food and water was the outstanding feature and it gave rise to a negative water balance in spite of some diminution in the water excretion.

3. In the final periods during which the three addicts were studied, after resumption of the drug, the food and water intake was approximately as in the first period. In two, addict 4 and addict 5, there was definite water retention; in neither addict 1 nor addict 4, however, did it in three days compensate for the previous loss.

4. When the water loss from skin and lungs is considered as a fraction of the total water loss through skin, lungs and urine, two addicts, nos. 1 and 3, exhibited initially a high loss of water through skin and lungs as compared with the controls. One can also recognize in three of the addicts, nos. 2, 4 and 5, a relatively greater loss through the skin and lungs during the withdrawal period.

Summary of Water Balance Studies in Normal Subjects and in Human Opium Addicts During Administration, Withdrawal and Readministration of Morphine *

Subject	Dates	Days in Period	Treatment	Change in Weight, Gm.	Food Intake: Protein, Gm.	Food Intake: Carbohydrates, Gm.	Food Intake: Fat, Gm.	Food Intake: Calories	Nitrogen Output, Urine and Feces, Gm.	Uric Acid in Urine, Mg.	Water of Oxidation of Food, Gm.	Total Water Intake, Gm.	Water Output of Urine, Gm.	Water Output of Skin and Lungs, Gm.	Total Water Output, Gm.	Water Balance, Gm.	$\frac{W_{s.l.}}{W_u + W_{s.l.}}$	Creatinine Coefficient, Urine
Control 1 (K. L.)	6/ 1 to 6/ 7/28	7	None	− 100 ± 3	102	235	141	2,750	16.6	441	321 ± 6	2975 ± 60	1885 ± 38	1080 ± 98	3059 ± 138	− 84 ± 198	0.36 ± .04	9.51
Control 2 (J. H.)	6/ 2 to 6/ 7/28	6	None	− 38 ± 3	102	235	141	2,750	16.0	464	323 ± 6	2982 ± 60	1720 ± 34	1231 ± 163	3007 ± 138	− 25 ± 198	0.42 ± .06	9.94
Control 3 (H. M.)	6/ 2 to 6/ 7/28	6	None	− 39 ± 3	102	235	141	2,750	16.2	565	322 ± 6	2982 ± 60	1830 ± 36	1118 ± 101	3003 ± 138	− 21 ± 198	0.38 ± .05	8.90
Addict 1 (M. C.)	3/21 to 3/27/28	5	With drug	− 85 ± 4	102	196	138	2,575	13.2	465	299 ± 6	2445 ± 49	1083 ± 22	1111 ± 99	2521 ± 128	− 76 ± 177	0.51 ± .05	8.08
	3/28 to 3/29/28	2	No drug	− 575 ± 10	102	196	138	2,575	16.6	964	299 ± 6	2414 ± 48	1367 ± 27	1468 ± 104	2942 ± 133	− 528 ± 181	0.51 ± .05	8.36
	3/30 to 4/ 1/28	3	With drug	+ 5 ± 7	102	196	138	2,575	16.5	535	299 ± 6	2570 ± 51	1340 ± 27	985 ± 101	2560 ± 133	+ 1 ± 184	0.42 ± .06	8.28
Addict 2 (V. W.)	3/23 to 3/27/28	5	With drug	+ 89 ± 4	101	196	138	2,550	15.8	428	299 ± 6	2442 ± 49	1302 ± 26	878 ± 99	2333 ± 128	+ 109 ± 177	0.40 ± .06	7.80
	3/28 to 3/29/28	2	No drug	−1121 ± 10	101	180	138	2,500	16.9	900	299 ± 6	1977 ± 40	1367 ± 27	1593 ± 96	3077 ± 125	−1100 ± 165	0.54 ± .06	7.07
Addict 3 (W. C.)	2/27 to 3/ 1/28	4	With drug	− 539 ± 5	102	178	135	2,450	16.7	...	290 ± 6	2747 ± 55	820 ± 16	2013 ± 113	3225 ± 135	− 478 ± 190	0.71 ± .07	
	3/ 2 to 3/ 4/28	3	No drug	−1494 ± 7	30	52	42	750	19.1	...	87 ± 2	1406 ± 28	707 ± 14	2093 ± 95	2856 ± 110	−1450 ± 138	0.75 ± .06	
Addict 4 (W. W.)	5/ 6 to 5/ 8/28	3	With drug	− 83 ± 7	104	235	141	2,775	15.4	361	325 ± 6	3163 ± 63	1882 ± 38	1036 ± 100	3250 ± 145	− 87 ± 208	0.36 ± .05	9.00
	5/ 9 to 5/10/28	2	No drug	−1004 ± 10	1.5	1.5	19	200	14.2	352	175 ± 4	1697 ± 34	1279 ± 26	1240 ± 91	2518 ± 119	−1339 ± 153	0.49 ± .05	6.71
	5/11 to 5/13/28	3	With drug	+ 690 ± 7	104	235	141	2,775	17.4	352	325 ± 6	2863 ± 57	1308 ± 26	787 ± 112	2162 ± 139	+ 701 ± 196	0.38 ± .08	8.20
Addict 5 (S. Z.)	5/ 6 to 5/ 8/28	3	With drug	− 149 ± 7	104	235	141	2,775	15.9	503	325 ± 6	2860 ± 57	1976 ± 40	978 ± 97	3016 ± 139	− 156 ± 196	0.32 ± .04	7.48
	5/ 9 to 5/10/28	2	No drug	− 908 ± 10	49	68	125	1,675	14.3	604	163 ± 3	1672 ± 33	1257 ± 25	925 ± 87	2503 ± 118	− 831 ± 151	0.42 ± .05	6.11
	5/11 to 5/13/28	3	With drug	+ 809 ± 7	104	235	141	2,775	16.3	377	325 ± 6	2863 ± 57	1187 ± 24	832 ± 114	2078 ± 139	+ 785 ± 196	0.41 ± .08	6.61

* Each calculation represents the mean per day for the period of study.

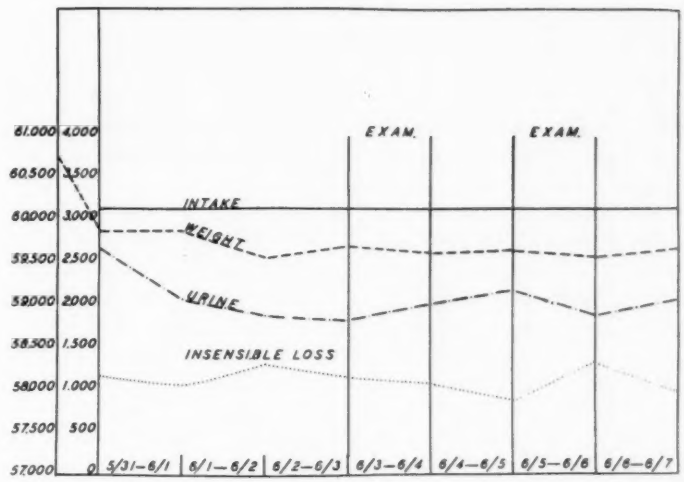

Chart 1.—Graphic representation of the daily intake of food, change in weight, urine output and invisible water loss of control 2. The ordinates represent grams.

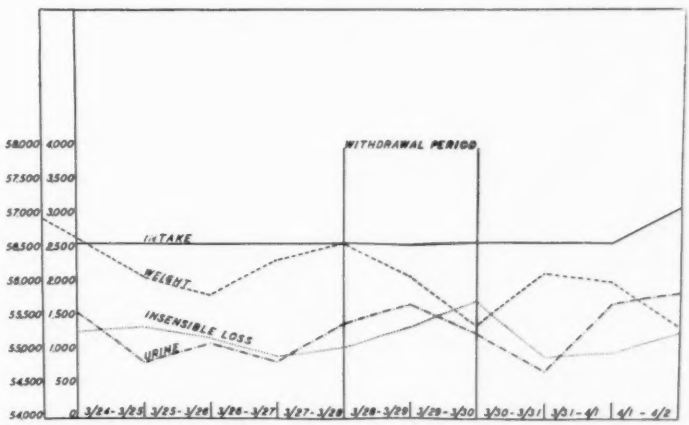

Chart 2.—Graphic representation of the daily intake of food, change in weight, urine output and insensible water loss of addict 1. The ordinates represent grams.

The explanation of this disturbance in the water balance during the period of withdrawal, had we only the data on addicts 3, 4 and 5, would naturally be the loss of water associated with inanition. This explanation hardly serves for the loss in addicts 1 and 2, unless we postulate an increased metabolism in these subjects during withdrawal. That such may well be the case seems not wholly improbable in view of the restlessness and nervousness of the individual patient during the withdrawal of the drug.

The output of nitrogen, as shown in the short periods studied, showed little or no change even when during the two days of withdrawal of morphine the food intake was curtailed. The output of uric acid shows in both addicts whose food intake during withdrawal was maintained, a definite rise.

All addicts during the first twenty-four hours of withdrawal showed a relative increase in the output of urine followed by a decided fall during the second twenty-four hours of this period. Water loss through skin and lungs, on the other hand, showed a relative increase during the second twenty-four hours compared with that during the initial twenty-four hours of withdrawal.

COMMENT

From the data available one can recognize a loss of weight and water during withdrawal. The tendency in three of the subjects to reduce the intake of food and fluid during the withdrawal period was undoubtedly a major factor in bringing this about. In two other subjects, whose food intake remained the same, the loss of weight was possibly an evidence of increased metabolism which may have had no further cause than the nervous restlessness of the individual patient at this time. That there was any more specific effect of the withdrawal of the drug on the water metabolism seems from the data obtained unlikely, but it cannot be absolutely excluded. To attempt a further answer by a study of withdrawal with the addict on a much higher level of caloric intake seems hopeless because of the aversion during withdrawal to even the moderate diet used in this study.

A marked increase in excretion of uric acid detected in addicts 1 and 2 with a constant diet, is noted in the table. All other addicts who served as subjects failed to maintain this constant intake. Studies of the uric acid of the blood in four other cases during withdrawal, however, failed to show any significant changes. Schubel [7] found an increased elimination of purine base and phosphoric acid during abrupt withdrawal in dogs; and attributed this to a sudden alteration in the

7. Schubel, Konrad: Stoffwechselversuche an Hunden während der Gewohnung an Morphin und während des Morphinhungers, Arch. f. exper. Path. u. Pharmakol. **88**:1, 1920.

central nervous system which he claimed took place following withdrawal of the drug. Sollier [8] attributed the symptoms accompanying withdrawal to marked alterations brought about in glands, particularly the endothelial cells, when morphine is no longer given.

The medical students who acted as normal subjects in these experiments were selected with a knowledge of their tendency to worry during examination. It is significant to know that these men retained their normal weight throughout the experiment, and failed to show a negative water balance or any increase in frequency or amount of urine on the two days on which the final examinations were given.

CONCLUSIONS

Abrupt withdrawal of morphine in a series of human addicts to opium resulted in a negative water balance and, in two of these subjects, an increased elimination of uric acid. The negative water balance was most likely due to failure to take sufficient food and water, although increased loss of water from increased metabolism cannot be entirely excluded, particularly in view of the restlessness of these subjects during withdrawal.

The control subjects, three medical students taking their first year final examinations, failed to show a negative water balance, any increase in frequency of urination or in twenty-four hour output, or any loss of weight on the days of the final examinations.

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8. Sollier, P.: La démorphinisation. Mécanisme physiologique. Conséquences au point de vue thérapeutique, Presse méd., April 23 and July 8, 1898.

HEPATOGENIC HYPOGLYCEMIA ASSOCIATED WITH PRIMARY LIVER CELL CARCINOMA*

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AND
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Deficient liver function has been assumed in certain cases of spontaneous hypoglycemia, but no proved examples of hepatic origin comparable with those apparently due to hyperinsulinism have been reported. The liver appears to be able to maintain an adequate blood sugar level in spite of widespread injury. Although complete removal is followed experimentally by a progressive fall in blood sugar, no marked change in carbohydrate metabolism has been observed after partial removal. The following case of hypoglycemia, apparently of hepatogenic type, is, therefore, of interest.

REPORT OF CASE

N. W., a colored man, a native of Honduras, aged 30, was admitted to the hospital for an exploratory laparotomy on July 6, 1928. He had been in good health prior to January, 1928, when he began to lose weight. In May, weakness was apparent; in June, he was seized with intense epigastric pain after eating. The pain decreased after an hour but a dull ache persisted for a week; there was no nausea or vomiting. Thereafter he had an occasional dull pain after meals and irregular periods of slight fever. On July 9, operation showed a hard, nodular mass the size of a large orange in the left lobe of the liver; a similar mass, the size of a walnut, was present in the right lobe. The pancreas, stomach, duodenum, gallbladder and kidneys appeared normal. Section of a small portion of tumor tissue was reported as adenocarcinoma. Sixteen days after operation, the patient was discharged.

On August 4, twenty-six days following operation, he was readmitted in a comatose state, from which he quickly aroused after administration of orange juice. He had had two previous spells of extreme weakness before breakfast, which were relieved by food. On the morning after admission the blood sugar during fasting was 0.04 per cent, and on the next day 0.053 per cent. Examination showed an emaciated negro, 68 inches (172.7 cm.) in height, weighing 113 pounds (51.3 Kg.). There was no evidence of jaundice. Slight general adenopathy was present. The thyroid gland appeared to be normal. The heart was normal in size, rate and rhythm; there was a systolic blow over the pulmonic area. The peripheral arteries seemed harder than normal. The blood pressure was 120 systolic and 84 diastolic. The lungs were normal except for a few scattered râles. A rounded, painless bulging, not definitely nodular, was present in

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the epigastrium, evidently in the left lobe of the liver, the smooth edge of which was palpated just above the navel. The spleen was not palpable; there was no ascitic fluid. The prostate was normal. The reflexes were normal. The blood count and smears showed only slight secondary anemia; the Wassermann and Kahn tests gave negative results. The urine was normal; the phthalein excretion was 45 per cent. The basal metabolic rate was minus 9 per cent. The results of the examination of the eyes were negative except for perivasculitis of the retinal vein. X-ray pictures of the skull showed a normal sella turcica and other bone structures.

Determinations of the blood sugar during fasting were subnormal. The collection of samples during strict fasting was prevented after a few days by the onset of coma, but specimens of blood obtained four hours and later two hours after feedings containing 18 Gm. of dextrose gave equally low readings (table).

Blood Sugar Determinations

	Blood Sugar (Mg. per 100 Cc.)	
8/ 6	40	fasting
8/ 8	53	
8/10	32	
8/11	52	five hours after 18 Gm. of dextrose
8/13	40	
8/16	27	
8/18	41	
8/20	44	
8/22	28	
8/24	33	
8/26	35	
8/28	40	
8/31	44	four hours after 18 Gm. of dextrose
9/ 2	47	
9/ 4	25	
9/ 6	37	
9/ 8	63	two hours after 18 Gm. of dextrose
9/10	43	
9/18	52	
9/21	49	
9/24	139	one hour after 18 Gm. of dextrose
9/27	81	
10/ 1	70	
10/ 5	114	
11/19	13	terminal

On August 14, tests made before meals and before supplementary feedings at 4 a. m. and at midnight (total dextrose 384 Gm.) showed a subnormal level in every instance except before the noon meal (fig. 1). Hypoglycemic attacks recurred during the early morning hours. A diet containing 440 Gm. of available dextrose (carbohydrate, 300; protein, 60; fat, 150) with supplementary feedings of 18 Gm. of dextrose at 3 and 9 a. m., at noon and at 4 and 10 p. m., also failed to prevent reactions. After September 13, the extra feedings were given hourly from 11 p. m. to 7 a. m. inclusive, and at 9 a. m. (total dextrose 510 Gm.). Finally, on October 9, because of occasional afternoon attacks, feedings at 3, 9 and 10 p. m. were added (total dextrose 570 Gm.). About this time the patient became unable to retain food; after October 16, he could take only irregular light meals and orange juice or dextrose, particularly at the onset of attacks. The afternoon temperatures rose from 99 or 100 to 100 or 101 F. During the intervals between attacks he was normal mentally and showed no toxic effects suggestive of hepatic insufficiency. The reactions became more frequent, occurring from three to seven times a day. They were all of the same character. The first subjective indication was a sense of fatigue followed by dimness of vision which caused the patient to lie down or, when already in bed, to lay aside whatever he was doing. There was no sense of discomfort. He would close his

eyes and forthwith lose consciousness. This phase was characterized by a peculiar staring expression, rolling of the eyes, grimacing and irregular movements of the arms and legs. The sclerae became blood streaked, and the pupils dilated. For some time he seemed to understand what was said to him, but there was no recollection of this afterward. The pharyngeal reflex was usually retained so that orange juice was swallowed when poured into the mouth. The respirations were not labored. The later attacks were associated with delirium. From an ordinarily mild mannered person he became noisy and resentful of his social status and treatment. Attacks of from ten to thirty minutes' duration were observed; they were promptly relieved by the oral administration of dextrose even though, late in the course, he would immediately spit out much of the orange juice. A blood pressure of 160 systolic and 110 diastolic observed during one attack had dropped to 140 systolic and 90 diastolic a few minutes after it was over. The final hypoglycemic reaction occurred on November 19. Dextrose was

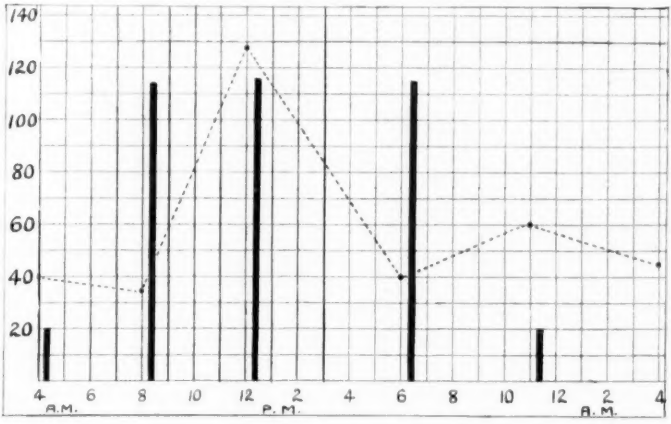

Fig. 1.—Diurnal blood sugar curve, taken on Aug. 13, 1928. The dextrose intake was 384 Gm. The curve represents the milligrams of blood sugar. The heavy black lines indicate the grams of dextrose in the diet.

withheld; through its use life had been prolonged to a point where the patient, unable to eat, passed from one shock to another as soon as the temporary effect of a little orange juice had subsided. Cheyne-Stokes' respirations appeared, a terminal blood sugar reading of 0.013 per cent was obtained, and death occurred from respiratory failure two and a half hours after the onset of the attack.

Clinical Studies.—On August 14, five hours after a feeding of 18 Gm. of dextrose, the blood sugar was 0.045 per cent; the administration of 88 Gm. of dextrose produced a maximal rise in the capillary blood to 0.209 per cent in one hour, with readings of 0.206 and 0.158 per cent, accompanied with traces of sugar in the urine after two and three hours, respectively. Tests repeated on September 1 with capillary blood and on September 4 with venous blood showed curves characterized by a rise from subnormal levels to 0.16 per cent in one hour and by a fall to subnormal levels within three hours, indicating a progressive decrease in tolerance (fig. 2). Fructose tolerance tests were not made.

On September 27, the injection of epinephrine (1 cc.) failed to produce an elevation in the blood sugar level. The initial blood sugar, about two hours after a feeding containing 18 Gm. of dextrose, was 0.081 per cent; one-half hour after the administration of epinephrine the reading was 0.057 per cent; in one hour 0.042 per cent and in two hours 0.022 per cent, at which point the patient became comatose. Pituitary extract produced no rise in blood sugar in one hour, at which point the administration of dextrose was necessary. The amylolytic activity of the stool was determined by Wohlgemuth's method as 110.8 and 62.5, on September 19 and October 23, respectively.

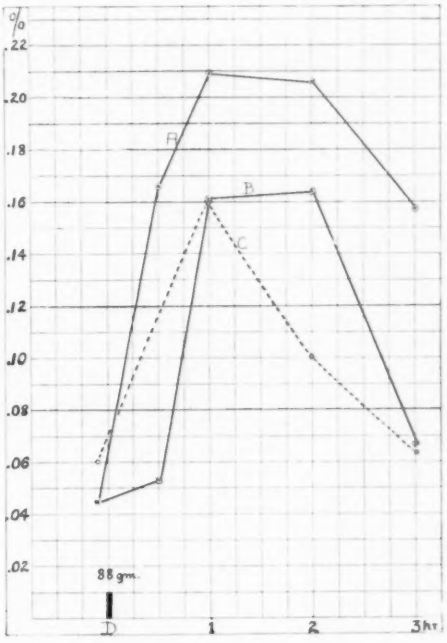

Fig. 2.—Curves for dextrose tolerance tests. *A* indicates the curve for the capillary blood taken on August 14; *B*, that for the capillary blood taken on September 1, and *C*, that for the venous blood taken on September 4. *D* indicates the amount of dextrose.

On August 22, the direct van den Bergh test was negative; quantitative determination showed less than 0.7 mg. per hundred cubic centimeters of serum. On September 1, the bromsulphalein test for liver function was normal. On the same date, the blood cholesterol was 176 mg. Estimations of the nonprotein nitrogenous constituents of the blood were not made.

The extraction of insulin from 50 cc. of the patient's blood as well as from 50 cc. of the blood of a normal control was attempted by Mr. I. J. Seitz of the Department of Physiology; none could be demonstrated in either extract by the Fisher modification of the Doisy, Somogyi and Shaffer method.

Necropsy Report.—The examination was conducted immediately after death by Dr. F. D. Gunn of the Department of Pathology. A summary of the important observations follows: The liver, weighing approximately 3,300 Gm., was distorted in shape; the left lobe, enlarged to about the same mass as the right, contained a nodular, rounded protuberance on its anterior and upper surface at about its middle; the remaining portions were studded with raised, rounded or umbilicated tumor nodules. Projecting from the anterior-inferior surface of the fundus of the gallbladder and covered only by peritoneum were two spherical tumor nodules about 1 cm. in diameter; several similar nodules occupied the loose connective tissue around the neck of the gallbladder and cystic duct. Otherwise, there was no involvement of the gallbladder and cystic duct; the extrahepatic

Fig. 3.—Section through the left lobe of the liver.

bile ducts were patent. An irregular tumor mass occupied the wall and a large part of the lumen of the inferior vena cava in the section surrounded by liver tissue. Sections through the liver showed the left lobe and middle portion practically entirely occupied by a more or less lobulated tumor mass, while the right lobe was partly filled with large and small tumor nodules, the remaining part of the liver substance lying at the extreme right portion (figs. 3 and 4). Roughly estimated approximately one fifth of the entire liver remained as such. The uninvolved portion was dark red brown, with markings somewhat exaggerated, rather firmer and tougher than normal.

Superficially the pancreas appeared normal, rather soft, and grayish yellow. On macroscopic examination, numerous sections failed to reveal any tumor masses or other pathologic changes. The spleen weighed 840 Gm. Its anterior

surface was rounded, of fairly firm consistency, and was dark purplish red. On section, the surface was smooth, homogeneous and rather dry; it was dark red, and the fibrous stoma was markedly increased; the follicles were not visible; no tumors were found on numerous sections. The brain was normal superficially and after preservation in fixative. The suprarenals were of about normal size, color and consistency; there was medullary substance in fair amount. The kidneys were about equal in size, smooth externally, with capsules stripping cleanly, leaving smooth pale surfaces. On section, the cortex, from 7 to 8 mm. in width, was moderately swollen and pale; the markings were distinct. The stomach, duodenum, small intestine and colon showed pale mucosa but no pathologic change; the mesentery was free from enlarged nodes and tumor masses; the

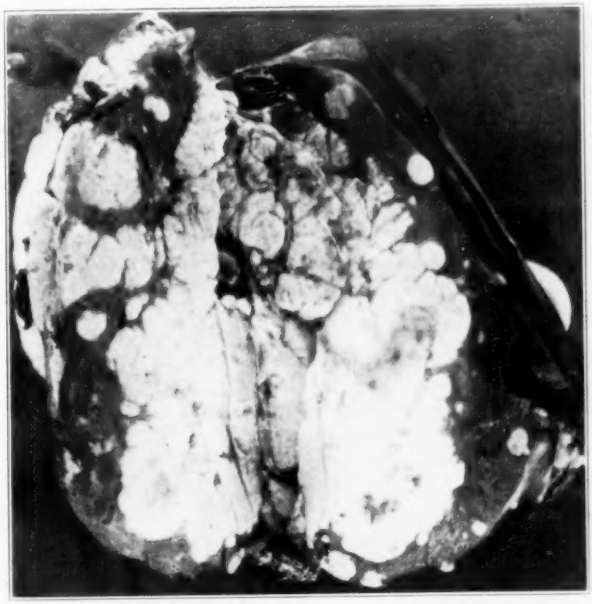

Fig. 4.—Section through the right lobe of the liver.

rectum was hyperemic and moderately edematous. The ureters, urinary bladder and prostate were normal in appearance.

The lungs contained numerous, evenly distributed nodules, ranging in size up to that of a walnut; those on the surface protruded prominently, while the larger ones were umbilicated. On section, the tumor masses were found distributed throughout the lung substance. The lung tissue between the nodules was well aerated except in the posterior portions which showed hypostasis and a moderate quantity of edematous fluid. The mediastinum, especially around the base of the heart, contained fairly numerous tumor-bearing lymph nodes ranging in size up to that of a hazelnut, two of the larger of which encroached on and lay partly in the posterior wall of the right atrium. The heart showed no pathologic change; the coronary arteries were patent and their lumina were of normal

diameters. The interior of the aorta showed linear and scattered, irregular, slightly raised yellow areas, especially in the ascending and transverse portions of the arch; the thoracic aorta was relatively free and the abdominal aorta was entirely smooth and normal in appearance. A small amount of clear amber fluid was present in the pleural cavity and in the pericardial sac; the abdominal cavity was partly filled with similar fluid.

Microscopic Observation; Section Stained with Hematoxylin and Eosin (Reported by Dr. F. D. Gunn).—In sections from the liver outside the tumor-bearing areas the larger number of liver cells were pale, swollen and rounded; many of them contained two or more large nuclei and in their cytoplasm there was a large quantity of golden brown granular pigment. In the tissue immediately adjacent to the tumor nodules the cells were compressed and atrophic; their nuclei were shrunken and pyknotic. There was a considerable quantity of dense fibrous tissue which partly separated the tumor from the parenchyma of the liver. In a few areas, the bile ducts showed a simple hyperplasia; elsewhere they appeared normal; even in places where completely surrounded by tumor cells their epithelial lining consisted of a single layer of cells, and the basement membrane was unbroken. Nowhere did the bile ducts appear to have taken on neoplastic characters.

Sections taken from the large tumor mass in the liver showed irregular cords, plugs of epithelial cells with a variable amount of fibrous tissue separating them from each other. Here there was a complete absence of the parenchyma of the liver. In many places the fibrous septums were broad, dense and hyalinized. The tumor cells were for the most part polyhedral, smaller and darker than the liver cells and arranged as thick cords, several cells deep, along the fairly rich network of capillary sinusoids (fig. 5). In other places the cells were large and clear with small, dark nuclei and arranged in small alveoli, separated from each other by thin fibrous septums, resembling, in many respects, hypernephroma.

Sections from the tumor masses of the lung closely resembled those in the liver. The nodules were sharply circumscribed and surrounded by thin fibrous capsules. In the large lymph nodes, the tumor nodules had a somewhat different appearance. The blood sinusoids, along the course of which the tumor cells were arranged, were wide. The fibrous stroma was abundant. The alveoli were much larger than elsewhere; their peripheries were sharply marked off by the blood sinusoids and in many places their centers were necrotic.

Sections taken from the head, middle and tail of the pancreas showed nothing remarkable. The islets of Langerhans appeared normal in size and number. In the spleen the reticulo-endothelial cells of the pulp were markedly increased in size and number, with atrophy of the lymphoid follicles and narrowing of the sinusoids of the pulp. Sections from the suprarenals showed nothing remarkable. Sections of the kidney showed a striking degree of necrosis and calcification of the cells of Henle's loops, while the remaining portions of the parenchyma appeared normal. A special study of the pancreas and tumor tissues was made possible by Prof. R. R. Bensley of the University of Chicago. In his opinion, the pancreas was normal and the tumor tissue from the liver was not islet tissue. There was neither an obvious increase of islet tissue nor an obvious change in the islets themselves; both A and B cells were present in about normal proportions and both were well charged with the characteristic secretory granules. The tumor tissue, tested both by Professor Bensley's neutral gentian stain and by Bowie's combination of ethyl violet and Biebricher scarlet, gave negative results as regards islet granules in both instances. There was, therefore, no indication of abnormal production of insulin by the cells of the neoplasm.

Analysis of Autopsy Material.—Prof. A. C. Ivy and Mr. I. J. Seitz of the Department of Physiology gave the following analyses:

Glycogen Content of the Liver: The liver weighed approximately 3,300 Gm., of which roughly 70 per cent was scirrhus. One hundred grams of liver tissue free from tumor nodules and an aliquot portion of the tumor were treated quantitatively for glycogen by the Pflüger method. The 100 Gm. of tumor tissue contained no glycogen; the 100 Gm. of liver tissue contained 0.8 Gm. of glycogen determined as dextrose.

Extraction of Insulin: The Fisher, Doisy, Somogyi, Shaffer method was used. Almost the entire pancreas (from 55 to 60 Gm.) was extracted for insulin and the final product dissolved in 40 cc. of water. Eight hundred grams of tumor

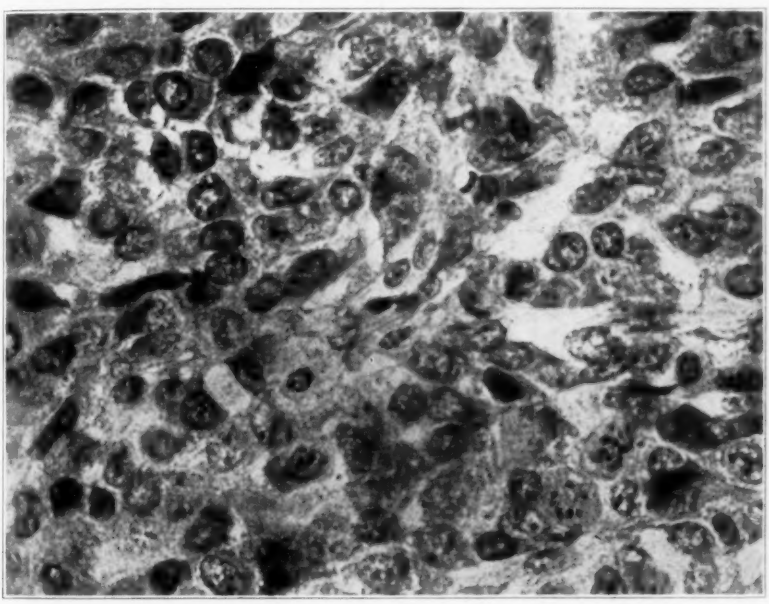

Fig. 5.—Tumor cells of the liver; × 800.

and a similar quantity of liver tissue were also extracted for insulin, and the final product of each was dissolved in 55 cc. of water. The usual method of assay was employed. The rabbits used weighed from 1,900 to 2,200 Gm. and were known by previous experience to react normally to insulin. The extract from the liver contained no insulin. The extract from the tumor likewise produced no insulin effect, and one rabbit responded to the subcutaneous administration of 5 cc. of the tumor extract with moderate hyperglycemia. The pancreas contained a minimal normal amount of insulin, about 100 units per kilogram.

COMMENT

The dominating anatomic feature of this case is a carcinoma which, so far as can be determined, is primary in the liver and of hepatic

cell origin. A large amount (from 70 to 80 per cent) of liver substance was replaced by the neoplasm. The remainder, if comprised of normally functioning cells, would be expected to maintain a glycogen storage balance, in view of the results reported by Mann [1] after experimental removal of part of the liver. The usual signs of hepatic insufficiency were lacking. Clinically, the hypoglycemia syndrome overshadowed all other symptoms. The course resembled in practically every respect the carefully studied case reported by Wilder,[2] which was due to overproduction of insulin, chiefly by liver metastases of a carcinoma primary in the pancreas.

Spontaneous hypoglycemia may be caused by either one of two opposing fundamental conditions, namely hyperinsulinism with excessive consumption of sugar or a deficiency in the glycogen storage or sugar mobilization function of the liver. The former, dependent on production of insulin, of necessity concerns the islands of the pancreas; the latter is concerned with the glycogen storage apparatus, chiefly the liver and muscles. Carcinoma and adenoma confined to the pancreas have caused fatal hypoglycemia,[3] and histologic studies have lent support to the view that spontaneous hyperinsulinism may occur. Wilder's case clearly demonstrates that tumor of the islets with metastases may lead to a fatal hypoglycemia due to hyperinsulinism. No comparable clinical picture of proved hepatic origin has been described. An hepatic origin has been assumed in various instances of spontaneous hypoglycemia, notably in the unusual case reported by Wagner and Parnas [4] in which instability of the blood sugar and negative results with epinephrine were interpreted as evidence of deficient sugar storage or lack of mobilizable glycogen. In various diseases of the liver, such as acute yellow atrophy and cirrhosis, terminal low blood sugar levels have been found. A fatal hypoglycemia appearing in the last weeks of a chronic, apparently infectious disease has been described in rabbits;[5] a progressive decrease in the effect of epinephrine was observed and a characteristic atrophy and fatty degeneration of the liver were found post mortem.

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1. Mann, F. C.: Effects of Complete and Partial Removal of Liver, Medicine **6**:419, 1927.

2. Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas: Hyperinsulinism and Hypoglycemia, J. A. M. A. **89**:348 (July 30) 1927.

3. Thalheimer, W., and Murphy, F. D.: Carcinoma of the Islands of the Pancreas; Hyperinsulinism and Hypoglycemia, J. A. M. A. **91**:89 (July 14) 1928. McClenahan, W. U., and Norris, G. W.: Adenoma of the Islands of Langerhans with Associated Hypoglycemia, Am. J. M. Sc. **77**:93, 1929.

4. Wagner, R., and Parnas, J. K., quoted by Wilder (footnote 2).

5. Oppel, W. W.: Zur Frage des hypoglykämischen Symptomenkomplexes bei Kaninchen, Ztschr. f. d. ges. exper. Med. **60**:86, 1928.

In the case presented hyperinsulinism can be ruled out since the pancreas was normal grossly and microscopically and since an assay of this organ yielded only a minimal normal amount of insulin. That the tumor cells had not exercised the function of islet cells is indicated by the failure to recover insulin from them and by histologic study.

We must conclude, therefore, that the hypoglycemia was due to a disturbance of the sugar mobilization function of the liver. The tumor contained no glycogen. The quantitative decrease in liver substance to 20 or 30 per cent was certainly an important but evidently not the only factor. After partial removal of the liver in dogs, resulting in a permanent reduction of hepatic tissue, in some cases to less than 15 per cent, Mann found only a slight change in the blood sugar level. Complete removal of the liver, however, is followed by characteristic symptoms associated with a progressive and fatal hypoglycemia; the end can be postponed for many hours by repeated injections of dextrose, but finally symptoms of another type appear which result in death even though the blood sugar level is maintained at, or above, a normal level.[1] Dogs with Eck-fistula develop loss of muscle coordination, staggering gait, weakness, disturbed vision, coma, convulsions and death, symptoms not unlike those of hypoglycemia but due in part to toxemia unrelated to carbohydrate metabolism since they can be relieved not only by dextrose but by Ringer's solution, atropine and gastric lavage.

In the case reported, the functional capacity of the remaining liver cells seems to have been the deciding factor. These cells were mostly pale, swollen and rounded, many containing two or more nuclei and a large quantity of brown pigment; the cells adjacent to the tumor tissue were definitely atrophic. Their glycogen content was unusually low (0.8 per cent). The conclusion seems justifiable, therefore, that in addition to a quantitative loss of liver substance a functional deficiency associated with an inadequate store of glycogen in the remaining cells was present, that the hypoglycemia was hepatogenic due to hypofunction of the residual cells. Under these conditions it is remarkable that symptoms suggestive of hepatic insufficiency, such as toxic manifestations of the type appearing in animals with Eck-fistula, did not appear and that the tests for liver function usually considered of greatest clinical value (the bilirubin content of the serum and the ability of the liver to excrete dye) were negative. The failure of epinephrine to produce a rise in the blood sugar and the abnormally high level produced by dextrose feeding suggested an inability of the liver to store dextrose but could not be considered decisive in view of the similar results in Wilder's case of hyperinsulinism in which the liver was gorged with glycogen.

SUMMARY

A case of spontaneous hypoglycemia, apparently of hepatic origin, is reported. Attacks of hypoglycemia dominated the clinical picture for three and a half months. Primary liver cell carcinoma, comprising roughly from 70 to 80 per cent of the total liver mass, with metastases in the regional glands, mediastinum and lungs, was found. The remaining liver structure was deficient in glycogen content and showed evidence microscopically of degenerative change. The pancreas contained a normal amount of insulin and presented no signs of pathologic changes. The tumor cells possessed no characteristics of islet cells and contained no insulin.

TUBERCULOSIS OF THE AORTA

REPORT OF A CASE *

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In 1882, Weigert [1] demonstrated the association between tuberculosis of the vascular system and acute miliary tuberculosis. The importance of these fundamental studies on tuberculosis of the vascular system is twofold. They demonstrated the damage resulting in the blood vessels themselves and made clear an important route by which tubercle bacilli are disseminated throughout the body.

While tuberculosis of the vascular system is relatively common, tuberculosis of the aorta is still regarded as a rare condition and one that is seldom diagnosed clinically. In reviewing the literature, I have been able to find thirty-six cases, including my own, reported since 1882. The reason the condition is not recognized clinically is that it does not appear to lead to any positive diagnostic signs or symptoms. The pathology, however, as well as the mechanism of the production of the lesion, is well known.

It is generally conceded that tubercle bacilli reach the aorta by one of two routes: first from the blood stream by direct implantation on the intima, or by the vasa vasorum, and second, from without, by the direct extension of a tuberculous process to the adventitia. Of the former type there have been sixteen cases reported, and of the latter, twenty cases, including mine.

The primary involvement of the vasa vasorum has not been demonstrated in man. The French writers Petit and Germain,[2] however, reported three cases of tuberculosis of the aorta in dogs, in which, they claimed, the primary lesions were in the vasa vasorum.

The condition resulting from direct implantation of tubercle bacilli on the intima of the aorta has been called tuberculous endaortitis. The lesions consist of large or small flattened nodules or, even more commonly, polypoid-like growths. Their development and course are similar to those of tuberculous processes elsewhere. Wooley,[3] in 1911, divided these primary intimal cases into acute and chronic endaortitis, and stressed as others have, the possible importance of the chronic type

* Submitted for publication, July 9, 1929.

* From the Pathological Laboratory, The Montreal General Hospital.

1. Weigert, P.: Virchows Arch. f. path. Anat. **88**:307, 1882.

2. Petit and Germain: Bull. soc. d'études sc. de la tuberc., 1911-1912; Arch. de méd. expér. et d'anat. path. **25**:469, 1913.

3. Wooley, P. G.: Bull. Johns Hopkins Hosp. **22**:82, 1911.

in the production of general military tuberculosis. He also suggested that the acute aortic lesions are a part rather than a source of general miliary tuberculosis, while the chronic cases may eventually lead to this condition.

Cases of chronic intimal tuberculosis have been reported by Benda,[4] Aschoff,[5] Longcope,[6] Schmorl,[7] Gaylord,[8] Simnitsky,[9] Lucksch[10] and Paisseau and Lambling.[11]

Cases of acute intimal tuberculosis include those reported by Marchand,[12] Huber,[12] Schuchardt,[13] Hanot,[14] Hanot and Levi,[15] Simnitsky,[9] Blumer,[16] Flexner[17] and Wooley.[3]

The cases in which the aortic involvement was due to extension from without are those reported by Dietrich,[18] Kamen,[19] Hanau and Sigg,[20] Schmorl,[7] Buttermilch,[21] Councilman and Mallory,[22] Leifmann,[23] Hedinger,[24] Ribbert,[25] Bauer,[26] Le Noble,[27] Dafoe,[28] Zrunek,[29] Kornitzer,[30] Vanzetti,[31] Mariani[32] and Garolamo Dal Lago.[33]

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29. Zrunek: Centralbl. f. allg. Path. u. path. Anat. **25**:577, 1914.
30. Kornitzer: Med. Klin. **16**:361, 1920.
31. Vanzetti: Arch. sc. medic., 1908.
32. Moriani: Virchows Arch. f. path. Anat. **202**:283, 1910.
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In the cases of Dietrich and Kamen the aorta was involved from adherent tuberculous bronchial lymph nodes, and in Kamen's case this was followed by rupture of the aorta and acute miliary tuberculosis.

In Buttermilch's case, the aortic involvement was secondary to vertebral disease. Schmorl reported two cases of perforation of the aorta as a result of a tuberculous process: one secondary to a tuberculous lymph node and another secondary to a tuberculous pulmonary cavity. In both, acute miliary tuberculosis resulted.

In Hanau and Sigg's case, a tuberculous aneurysm ruptured into a tuberculous cavity in the lung.

Councilman and Mallory demonstrated a false aneurysm of the thoracic aorta secondary to extension from a tuberculous lymph node, from which acute miliary tuberculosis resulted.

Leifmann demonstrated a case of rupture of the aorta secondary to a caseous mediastinal lymph node, in which acute miliary tuberculosis developed.

Hedinger's patient had tuberculosis of the adventitia associated with subacute milary tuberculosis, tuberculous basilar meningitis and a solitary tuberculous nodule in the cerebellum.

Ribbert's paper dealt with a case in which there was a communication between the lumen of the aorta and a tuberculous cavity in the lung, which was secondary to tuberculosis of the vertebrae. General miliary tuberculosis followed.

Zruneck described a case of tuberculosis involving the abdominal aorta in the region of the celiac axis, which led to rupture and death.

In 1920, Kornitzer reviewed eleven cases of ruptured tuberculous aneurysms that had been reported up to that date, and added a case of Professor Stoerk's of Vienna. Stoerk's case was one of rupture of the ascending aorta 1 cm. beyond the aortic cusps and was due to a tuberculous process which began in a group of adjacent lymph nodes. The edges of the rupture were thinned, and the walls of the aneurysms showed an extensive tuberculous process involving two thirds of the media.

Vanzetti's paper, published in 1908, was based on a case of ruptured tuberculous aneurysm of the arch of the aorta, which originated from a tuberculous process in the vertebra and infiltrated the posterior mediastinum. The aortic wall was involved over a considerable area, and at one point the process reached as far as the outer border of the intima and at other points, to the internal layers of the media. Opposite the tuberculous area of the aortic wall was a large prevertebral caseous mass.

Mariani described a case of tuberculosis of the ascending arch of the aorta following tuberculous pericarditis. The process extended for some distance beyond the pericardium. There was an associated hyperplasia of the intima. The media was weakened functionally, and "bulging" had occurred.

In 1913, Gerolamo Dal Lago reviewed the literature and added the report of a case of tuberculous mediastinitis in a young patient, which infiltrated the esophageal and aortic walls, leading to the formation of an esophageal ulcer and subsequently to an esophageal-aortic fistula. Death resulted from hemorrhage.

Bauer found an extension of tuberculosis of a lymph node to the arch of the aorta.

LeNoble described a tuberculous aneurysm of the first portion of the aorta.

Dafoe reported two cases of ruptured aneurysm of the abdominal aorta due to tuberculosis.

My case is the twentieth recorded case of tuberculosis of the aorta due to direct extension from without.

REPORT OF CASE

History.—A man, aged 56, a laborer, born in Canada, was admitted to the Montreal General Hospital in the service of Dr. Campbell P. Howard on Nov. 15, 1927, complaining of "swelling of the legs; cough; pain in the right side; itchiness of the skin; yellow vision; shortness of breath; occasional coldness, whiteness and loss of sensation in the distal phalanges of both hands."

One sister had died of pulmonary tuberculosis. His wife, who had died of probable angina pectoris at the age of 55, had had eleven pregnancies, one of which terminated in miscarriage; nine children died in infancy, and one was alive and well.

The patient had not worked for the past two years. He had smallpox as a child. There was no history of syphilis. A cough, unaccompanied by pains in the chest or expectoration, had been present ever since he could remember. He had complained of occasional swelling of the feet and ankles which would disappear over night.

The present illness began about April, 1927, with loss of appetite and a marked swelling of the feet and legs. Soon after, shortness of breath appeared and became a distressing symptom; pain in the left side of the chest developed; this grew worse when he coughed. About this time, a small amount of blood was coughed up. Later, pain was felt over the right side of the chest; this had persisted.

Because all the symptoms were progressing in spite of rest at home, he was admitted to the hospital in November, 1927, seven months after the onset of the present illness.

Physical Examination (Dr. C. P. Howard).—The patient was sallow, dyspneic and orthopneic; he coughed frequently but did not expectorate. The mucous membranes were pale and cyanotic. The lymphatic system was normal. The thorax was of the long type, with bony landmarks and deep infraclavicular and supraclavicular fossae. The back was bowed. The upper part of the left side of the chest, anteriorly, was definitely flatter than the right, and expansion here was practically nil. Tactile fremitus was diminished in the left axilla. The percussion note was impaired on the left from the second rib to the base of the axilla and over the base posteriorly. Resonance was present on the right, but the note was impaired over the base. Over the areas of dulness, the breath sounds and vocal resonance were suppressed. Elsewhere, there were many fine moist râles. The pulse rate was rapid, 90 per minute, regular and of small volume. The vessel wall was just palpable. The blood pressure was 145 systolic and 102 diastolic. There was a slight precordial fulness of the heart, but no visible pulsation. The point of maximum impulse could be best felt in the fifth interspace, 12 cm. from the midline. The relative cardiac dulness extended to the level of the second interspace above,

6 cm. to the right and 15 cm. to the left of the midline. The heart sounds were distant. No murmurs or accentuations were made out, but there was a tendency to gallop rhythm. The remainder of the physical examination showed nothing of importance, except some edema of the legs and feet.

The blood count showed: red blood cells, 4,310,000; white blood cells, 7,200; hemoglobin, 50 per cent. The differential count gave: polymorphonuclears, 74 per cent; lymphocytes, 25 per cent and eosinophils, 1 per cent.

On Nov. 17, 1927, Dr. Richie made the following report of the roentgen examination of the chest. "The heart appears to be increased in the transverse diameter, the arch of the aorta widened. There is evidence of a collection of fluid at both bases, more marked on the left side than on the right. The other shadows seen throughout the lung fields are, I believe, secondary to the cardiac condition rather than due to any definite infection."

The electrocardiogram showed inversion of the T wave. The urea concentration factor was only 18. The Wassermann reaction of the blood was 3 plus on two occasions. The fundi showed one or two scattered hemorrhages.

During the patient's stay in the hospital, a period of five months, the clinical signs and symptoms, as well as the general appearance, varied from time to time, yet there was gradual failure and certain features were always prominent: precordial pain; nocturnal paroxysms of dyspnea; evidence of decompensation of the heart, necessitating bleeding and repeated courses of digitalis; the presence of chronic nephritis at laboratory examination, which gradually became more and more pronounced; an enlarged and tender liver; a sallow color; dilatation of the arch of the aorta and a 3 plus Wassermann reaction on two occasions. A pericardial friction rub, though suspected and often looked for, was present on only one occasion.

The clinical and laboratory observations, apart from those concerning the progressive chronic nephritis, are of special interest with reference to the postmortem examination. The nocturnal paroxysms of dyspnea, the precordial pain, widening of the arch of the aorta, the positive Wassermann reaction and the sallow complexion strongly suggested syphilis of the aorta as one of the pathologic conditions.

The final clinical impression of the case was: (1) chronic interstitial nephritis, (2) aortitis syphilitica, (3) cardiac decompensation and (4) auricular fibrillation.

Autopsy.—The anatomic diagnosis was as follows: (1) hypertrophy of the heart; (2) chronic diffuse nephritis; (3) tuberculosis of the lungs, pleura (left), peribronchial and mediastinal lymph glands, pericardium and aorta; (4) tuberculous pleural effusion (right); (5) chronic passive congestion of the lungs, liver and spleen; (6) acute congestion of the cerebral vessels, and (7) arteriosclerosis of the aorta (slight).

Pathologic examination revealed the following: Macroscopically, the heart was increased in size and weight. The greatest transverse diameter was 15 cm. in situ, while the weight, with the pericardium attached, was 830 Gm. There were old fibrous adhesions between the pericardium and both pleurae, more marked on the left side. The pericardial cavity was completely obliterated by fibrous adhesions, in which blood vessels were quite numerous. While the obliteration of the sac was complete, the density of the adhesions which led to it varied. They were most dense over the apical regions and at the base. When the two layers of the pericardium were forcibly separated, a great many small, grayish, discrete and confluent tubercles were visible. They were not uniformly distributed, but occurred in large and small irregularly outlined areas. Collectively, they were most numerous throughout the apical region. No gross caseation was seen. The

mediastinal lymph glands were deeply pigmented with carbon, and some of them showed a tuberculous process. The left side of the heart was markedly hypertrophied, and the right side was dilated. The valve measurements were: tricuspid, 14 cm.; pulmonary, 9 cm.; mitral, 10 cm.; aortic, 7 cm.; eustachian, 2.5 cm., and coronary, 1 cm. The tricuspid valve was slightly increased in circumference, while the aortic ring was neither enlarged nor thickened. The musculature was of a uniform, pale brown and was firm in consistency. The valves and endocardium were normal. The coronary arteries were patent throughout. Beyond the pericardial cavity, there was no gross evidence of tuberculous involvement of the great vessels of the heart or the tissues immediately about them.

The first portion of the aorta showed the intima to be smooth and glistening with only a few small, noncalcareous plaques about the orifices of the coronary

Fig. 1.—Tuberculosis of the pericardium. Section through the parietal and visceral layers, including the heart muscle. The obliteration of the pericardial sac should be noted.

vessels. In the lower abdominal portion of the aorta, there were also a few raised, yellowish plaques. At no place was there wrinkling or stellate scars visible in the intima, suggesting syphilis.

Microscopic examination of the heart (figs. 1 and 2) revealed the following: The two layers of the pericardium were united by a mass of inflammatory granulation tissue which was undergoing organization and had led to obliteration of the pericardial sac. The visceral layer was greatly thickened and edematous and showed on its inner surface tuberculous granulation tissue with numerous characteristic tubercles. Tubercle bacilli were demonstrated within the caseous areas. The muscular fibers were uniformly increased in size and showed indistinct markings of the cross striations. There was no evidence of fibrosis.

Numerous sections were taken from various levels of the aorta. Those taken from the first portion, within 3 cm. of the aortic ring and immediately beyond the level of the pericardial reflection, showed the intima regular in outline and well preserved. There was no scarring or round cell infiltration about the vasa vasorum in the adventitia to suggest syphilis. The adventitia, as well as the periadventitia, showed inflammatory granulation tissue, with characteristic tubercle formation and numerous giant cells (figs. 3 and 4). At one point (fig. 5), this tuberculous process involved the outer portion of the media. Tubercle bacilli were demonstrated in this tissue. Verhoff elastic tissue stain showed no lesion of the vasa vasorum. Sections taken from various other levels, including the abdominal portion, showed no evidence of syphilis or tuberculosis. There was only a moderate arteriosclerosis.

The right lung weighed 700 Gm. It was mottled and grayish-black; its

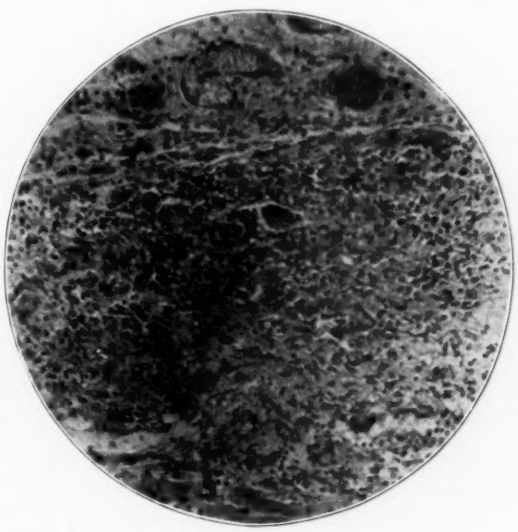

Fig. 2.—Tuberculous lesion of the pericardium. The giant cells and the tuberculous granulation tissue should be noted. High power magnification.

pleura was smooth, moist and glistening, except for a puckered scar 3 cm. in diameter at the apex, and a few recent tubercles at the base. The lung was collapsed and subcrepitant throughout. Serial sections from 1 to 2 cm. thick, made throughout the lung from apex to base, after fixation, showed slight compensatory emphysema of the upper lobe. The lymph nodes at the hilum were slightly increased in size, deeply pigmented with carbon and showed caseous tuberculosis.

The left lung weighed 800 Gm. There was obliteration of the left pleural cavity which had, in part, resulted from fibrous adhesions of the two surfaces and in part from a fairly acute exudative process. The fibrous adhesions were most marked throughout the apical region, the anterolateral aspect and along the under surface of the lung where it was firmly bound to the diaphragm. The acute exudative tuberculous process was most marked throughout the posterior aspect and was reflected on to the superior surface of the diaphragm posteriorly. The

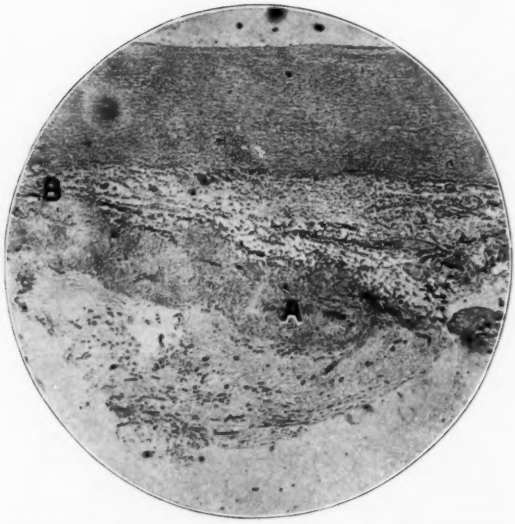

Fig. 3.—A transverse section through the aorta and the periaortic tissues. *A* indicates the large tuberculous area in the periaortic tissues and *B*, the tuberculous involvement of the adventitia.

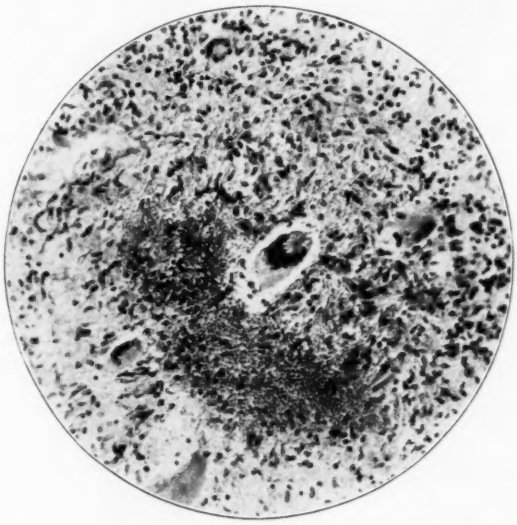

Fig. 4.—High power magnification of figure 3 at *A*. The giant cells and tuberculous tissues should be noted.

acute process showed a thick, rather dry, friable, semicaseous material which covered, as a continuous sheet, the visceral layer of the pleura and the parietal layer opposite it. This thick exudate could be readily scraped off. The pleura of this lung was thickened throughout, because of a definite increase in fibrous connective tissue. It was not only increased in consistency, but in some areas it was almost cartilaginous. Serial transverse sections from 1 to 2 cm. thick, from apex to base, after fixation showed a marked anthracosis irregularly distributed throughout the lung. In the upper lobe, about its center and 4 cm. from its apex, there was a sharply outlined, pale, grayish-white, firm tuberculous nodule, 3 mm. in diameter, with a well demarcated peripherial zone composed of deeply pigmented, dense, homogeneous connective tissue. There was a similar area in the lower lobe near one of the secondary bronchi. None of the foci showed calcification. After careful search with a hand lens, no other gross tuberculous foci were demonstrated

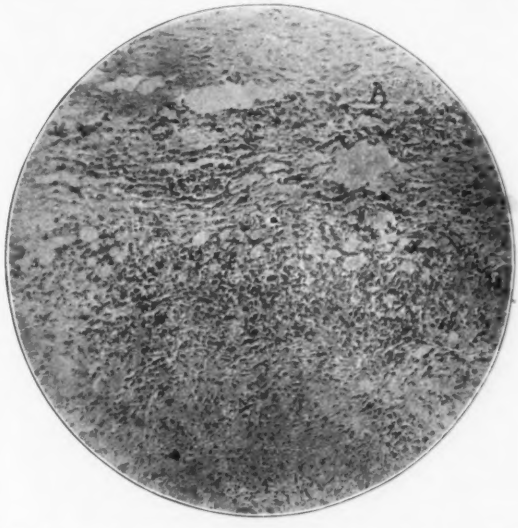

Fig. 5.—Tuberculosis of the adventitia. The margin of the media is shown at *A*.

in the lungs. The peribronchial lymph nodes were deeply pigmented with carbon and showed caseous tuberculosis.

Microscopic examination of sections from the lungs showed marked congestion and partial atelectasis of the right lung. The left lung showed tuberculosis of the pleura, marked edema and congestion and one microscopic tubercle in the lung parenchyma. Sections from the peribronchial glands showed areas of caseous tuberculosis in which tubercle bacilli were demonstrated.

COMMENT

This case falls readily into the second group of lesions of tuberculosis of the aorta, namely, that due to direct extension from outside the vessel wall. However, it presents several interesting features,

some of which were not referred to in the cases previously reported. Acute miliary tuberculosis was not present. The lesion in the aorta was not of sufficient extent to lead to perforation and its accompanying miliary tuberculosis. Pulmonary tuberculosis was found, not as an active ulcerative form, but as old healed apical scars with two small caseous nodules, while the microscopic examination revealed a third isolated tubercle. On the other hand, there was an extensive acute tuberculous involvement of the left pleura and dense fibrous adhesions obliterating the pleural cavity and extending to the pericardium. The peribronchial and mediastinal lymph nodes and the pericardium also showed an active tuberculous process. It seems quite reasonable to suppose that the tuberculous process started originally in the lung, and then involved the pleura, the bronchial and mediastinal group of lymph nodes, as well as the pericardium and periaortic tissue, and finally the aorta itself. In the other somewhat similar cases reported, with the exception of Mariani's, a tuberculous mass or a tuberculous lymph node was always found attached to or in the vicinity of the aorta. In this case, however, no gross tuberculous tissue could be found attached to the aorta, outside the pericardial cavity, and it was only after a microscopic examination of the aorta that the true condition was revealed. This tuberculous process was found limited to the first portion of the aorta. The most interesting features clinically were the signs and symptoms that led to the diagnosis of aortitis syphilitica; namely, the history, the paroxysms of dyspnea, the precordial pain, the positive Wassermann reaction and the x-ray report of widening of the arch of the aorta. The similarity of the signs and symptoms to syphilis of the aorta might be explained by the site and character of the lesion and the fact that clinical signs and symptoms may depend more on gross lesions than on the action of any specific toxin.

SUMMARY

1. Thirty-six cases of tuberculosis of the aorta have been reported.

2. The case cited here is the twentieth reported instance of tuberculosis reaching the aorta by extension from a tuberculous process outside the aorta.

3. In this case the involvement extended to the media, but no rupture occurred.

4. Clinically, syphilitic aortitis was suspected on account of the history, shortness of breath, pain, pallor and the positive Wassermann reaction.

BOECK'S SARCOID

REPORT OF A CASE WITH VISCERAL INVOLVEMENT *

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PHILADELPHIA

Reports of Boeck's sarcoid with visceral involvement are uncommon. When on postmortem examination of our patient it was noted that lesions similar to those of the skin co-existed in the epicardium, in the bronchial mucosa and in the mucosa of the ileum, the problem of the etiology of the malady and its significance to internal medicine was brought anew to our attention.

BOECK'S SARCOID

In 1899, Boeck [1] for the first time described a cutaneous malady which since has been known as Boeck's sarcoid. In 1900,[2] he described three additional cases of it. The disease is chronic and it is characterized by the presence on the skin of either small or large nodules or infiltrated plaques, varying in number from one to many hundreds. These lesions occur usually at some point on the face; whence they may spread to other parts of the face and may gradually involve the extremities and the trunk. Each single papule or nodule requires months, sometimes years, for its development and for the various stages of its course. The efflorescence may appear under various aspects. Often the eruption appears suddenly, the skin being red and swollen and the seat of an itching sensation. In other cases, a distinct papule appears on the affected skin surface; sometimes the papule is only felt under the skin. The nodule or plaque is usually bright red, bluish red or brownish red. Later in the course, it is bluish red in the center and yellowish brown at the periphery. The nodule or plaque may involute without therapeutic intervention, leaving a pigmented atrophic scar. This may last for a

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1. Boeck, C.: Multiple Benign Sarcoid of the Skin, J. Cutan. Dis. **17**:543, 1899.

2. Boeck, C.: Abstr., J. Cutan. Dis. **20**:38, 1902.

long time and is a characteristic phase of the malady. The nodule or plaque may also show a network of capillaries in the central area. The nodule feels hard, and often, on pressure with a glass slide, shows a minute yellow focus; this led to the name of miliary lupoid. The latter term is more desirable, as the term sarcoid is unwarranted, the resemblance to sarcoma, if any, being remote.

Darier,[3] from the study of the records of cases in the literature, divided sarcoids into four groups as follows: (1) the multiple benign sarcoid of Boeck; (2) the subcutaneous sarcoid of Darier and Roussy; (3) the nodular erythematous induration-like sarcoid of the extremities, and (4) the Spiegle Fendt sarcoid. This classification was at one time adhered to by dermatologists and still may be found in all textbooks on cutaneous diseases. However, at present, of the four groups, Boeck's sarcoid and Darier and Roussy's sarcoid are the only two types that are accepted by dermatologists as clinical entities. Treatment is ineffective, except that under prolonged use of arsenic the lesions involute. There is a strong suggestion of coincidence: one of the characteristics of this efflorescence is that the lesions disappear leaving atrophic pigmented spots, without therapeutic intercession.

ETIOLOGY

With the report of our case, it was our intention to review the literature related to the subject. This has been done completely by Goeckerman.[4] His careful résumé of the observations on sarcoid and related lesions throws the entire subject into relief and serves as a background for the proper appraisement of what is known and also what is still in controversy with regard to the etiology of the sarcoid.

Reschin,[5] as well as Kuznitzky and Bittorf,[6] considered the condition as a definite disease entity. On the other hand, many investigators view the sarcoid as a symptomatic manifestation of various diseases. However, the ruling thought appears to be that Boeck's sarcoid is caused by the tubercle bacillus and that the cutaneous lesion is a manifestation of sensitization in a patient whose epithelial cells have previously been sensitized to a tuberculous antigen. The clinical appearances that the lesion may assume and its morphologic variation from other tuberculous lesions

3. Darier, J.: Die cutanen und subcutanen Sarcoid: Ihre Beziehungen zum Sarcom zur Lymphodermie, zur Tuberkulose, Monatshr. f. prakt. Dermat. **1**:419, 1910.

4. Goeckerman, W. H.: Sarcoids and Related Lesions, Arch. Dermat. & Syph. **18**:237 (Aug.) 1928.

5. Reschin, M.: Universelles benignes Miliarlupoid, Boeck's mit Beteiligung innerer Organe, Arch. f. Dermat. u. Syph. **139**:30, 1922.

6. Kuznitzky, E., and Bittorf, A.: Boecksches Sarkoid mit Beteiligung innerer Organe, München. med. Wchnschr. **62**:1349, 1915.

of the skin depend on the manner in which the particular patient reacts to the tuberculous antigen. An attentive reading of the literature with reference to the etiology of the disease seems to favor tuberculosis as the origin of Boeck's sarcoid. Nevertheless, a notable point is scored by those who are opposed to the hypothesis that the condition is tuberculous. They stress the failure, except in a few cases, to demonstrate the acid-fast organism in the lesion. Those who favor the theory that the lesion is tuberculous point to Kyrle's investigations as indispensable, if one is to understand the conditions under which the lesion is brought about. It was Kyrle's [7] concept that the sarcoid is a distinct type of foreign body reaction to the bacillus of tuberculosis and its disintegration products. He attributed the difficulty of finding the tubercle bacillus in sections of the sarcoid and following its inoculation into animals to the fact that the bacillus is of low virulence and the allergy in such cases rather high. Kyrle's microscopic studies are illuminating: Within the first ten days, the changes caused by the invasion of the skin by the bacillus of tuberculosis consisted of a simple inflammation and the presence of numerous tubercle bacilli in the infiltrate. At the end of twenty-one days, endothelial cells made their appearance and became encapsulated. At the same time, the tubercle bacilli gradually began to diminish in number. After thirty-six days, the tubercle bacilli could not be demonstrated microscopically, but the histologic picture described first by Boeck and considered by him characteristic of the disease was noted by Kyrle. Other investigators who were able to show the presence of tubercle bacilli in early lesions were Wende [8] and Ruete.[9]

The inadequacy of the assumption of Kuznitzky and Bittorf and Reschin that Boeck's sarcoid is a disease entity is made obvious by the studies of Kyrle, Schamnon, Lutz, Bank, Block, Jungling, Jans, Lewandowsky and Goeckerman.[4] These investigators are several among many who found systemic lesions either in lungs or bones (fibrocysts) or in some other anatomic structure of their patients. The presence of tuberculosis in many of the patients and the microscopic and clinical resemblance of the sarcoid to tuberculosis were considered by them as conclusive evidence that the cause of Boeck's sarcoid is tuberculosis, and therefore they could not regard it as a disease entity.

Syphilis as a Cause.—Most studies of the etiology of Boeck's sarcoid are concerned with the presence of a concomitant tuberculosis. As

7. Kyrle, J.: Die Anfangsstadien des Boeckschen Lupoids; Beitrag zur Frage der tuberkulosen Aetiologie dieser Dermatose, Arch. f. Dermat. u. Syph. **131**:33, 1921.

8. Wende, G. W.: Nodular Tuberculosis of the Hypoderm, J. Cutan. Dis. **29**:1, 1911.

9. Ruete, A.: Zur Aetiologie der Boeckschen Erkrankung, Dermat. Ztschr. **37**:129, 1922-1923.

a result, the possible presence of systemic lesions is often overlooked. Frost's [10] third patient is a case in point. The patient had lesions of the skin on one of her fingers. A roentgenogram of the chest showed increased prominence of the lung markings, leading from the hilum to an area in the upper lobe of the left lung. In this area there were a few discrete patches of increased density from about 0.5 to 1 cm. in diameter. The author assumed that these discrete patches of increased density were evidence possibly of active tuberculosis. It is generally accepted that marmoration or infiltration of the lungs, beginning at the roots and spreading toward the bases or upward, and associated with clear apexes, is not common in tuberculosis, but is consistent with syphilis, and from the clinical observations and the study of the literature by one of us (D. M. S.) it was found that when patchy, discrete infiltrations of the lungs are associated with Boeck's sarcoid, they are sarcoid lesions.

Notwithstanding the allusion to tuberculosis as a single cause, we believe, nevertheless, that syphilis shares in the causative responsibility for some of the cases. As in tuberculosis, so in syphilis, the organisms can be found in early lesions, but seldom, if ever, in late lesions. Furthermore, *Treponema pallidum* and the tubercle bacillus have one point in common, namely, that they produce multiform lesions which may resemble one another. The tuberculosyphilid resembles tuberculosis of the skin microscopically and clinically. Evolution of the lesion, which is a tuberculous infiltration of the true skin with gummatous material, is by circumferential growth of new tubercles. Those first formed disappear, leaving scars without previously ulcerating. The syphilid is maintained by the successive outcrop of new tubercles, and a single patch may thus be prolonged for years. If one accepts Kyrle's explanation of the cause of sarcoid by the tubercle bacillus and its disintegration products as a distinct type of foreign body reaction, then it must be conceded that *Treponema pallidum* possesses the same potentialities under similar favorable conditions. The following facts indicate that our patient had syphilis and not tuberculosis. In the latter disease there is often considerable involvement of the lungs without dyspnea, but in syphilis of the lungs, dyspnea is a prominent symptom. The productive cough and the expectoration, which, at times, was tinged with blood, would indicate chronic pulmonary tuberculosis. Yet repeated examinations of the sputum revealed no tubercle bacilli. Incidentally, the bloody sputum was caused by bronchial lesions, which were represented by small hemorrhagic patches, and the excruciating abdominal pain and constipation were due to ulcers of the overlying mucosa of

10. Frost, K. P.: Sarcoid of Boeck, Arch. Dermat. & Syph. **13**:389 (March) 1926.

the intestines. The evidences of syphilis in our patient, to which we attach most weight, were the strongly positive Wassermann reaction obtained with both the blood and the pleural fluid, the areas of perivascular and perineural mononuclear infiltration and the independent collections of mononuclear cells in the liver and elsewhere.

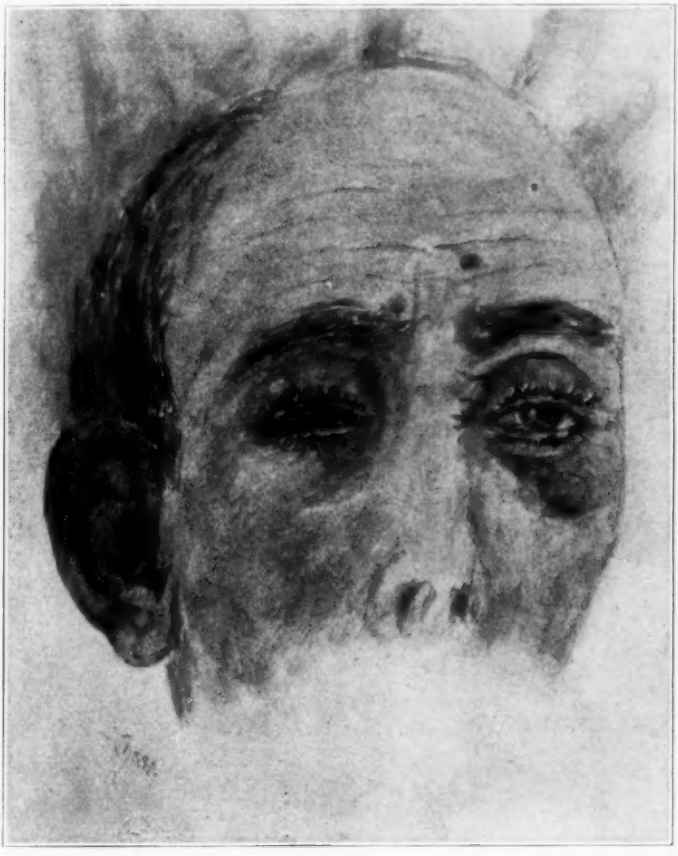

Fig. 1.—Boeck's sarcoid appearing in the ear, on the eyelid and on other parts of the face.

REPORT OF CASE

A white man, aged 52, a Russian Jew by birth and a tailor by occupation, was first seen by one of us (M. B.) in June, 1926. At that time, he complained of weakness and of the presence of purplish lesions, which had appeared two months before, in the ears, on the eyelids and other parts of the face and on the trûnk. A marked cyanosis of the lips and the face suggested a possible polycythemia, but

as the red cell count was normal, this diagnosis was discarded. When the patient was seen two months later, he had grown considerably weaker, and a productive cough and expectoration that at times was tinged with blood had developed. He was also dyspneic. The cutaneous lesions were more numerous and consisted of infiltrated plaques, papules and nodules. The lesions were firm and elastic and

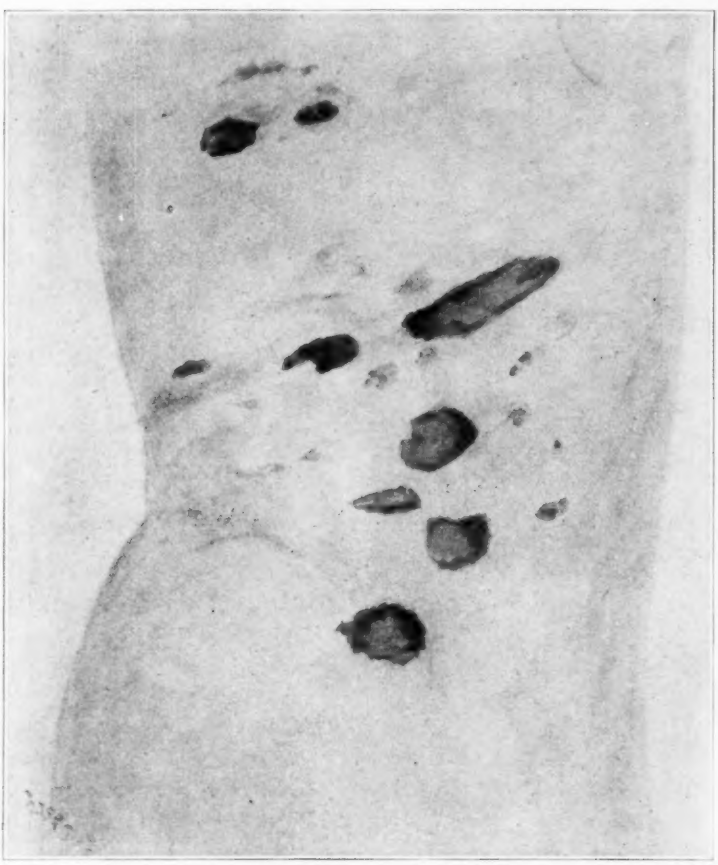

Fig. 2.—Boeck's sarcoid appearing on the body as plaques, papules and nodules, firm, elastic and purplish.

were purplish. Some of these lesions had a reddish tint and presented a delicate central telangiectasis. None of the lesions showed any tendency toward ulceration. The diagnosis of Boeck's sarcoid was made. A section from one of the lesions was excised, prepared and stained in the usual manner for microscopic study. The microscopic sections showed the presence of sharply circumscribed, deep-seated nodules, which were separated from one another by connective tissue

septums. The cells comprised epithelioid cells with faintly staining nuclei, lymphocytic plasma cells and a few giant cells.

The examination of the chest revealed signs of a bilateral hydrothorax, which extended to the fifth rib posteriorly on the right side and to the sixth rib posteriorly on the left side. Roentgen examination confirmed the presence of the bilateral hydrothorax; otherwise the report was negative.

The patient's dyspnea became rapidly worse and the pleural fluid was aspirated. In the course of three months, the chest was tapped twelve times: seven times on the right side, for a total of 4,585 cc. of pleural fluid, and five times on the left, for a total of 4,945 cc. of fluid. The fluid was dark yellow and on several

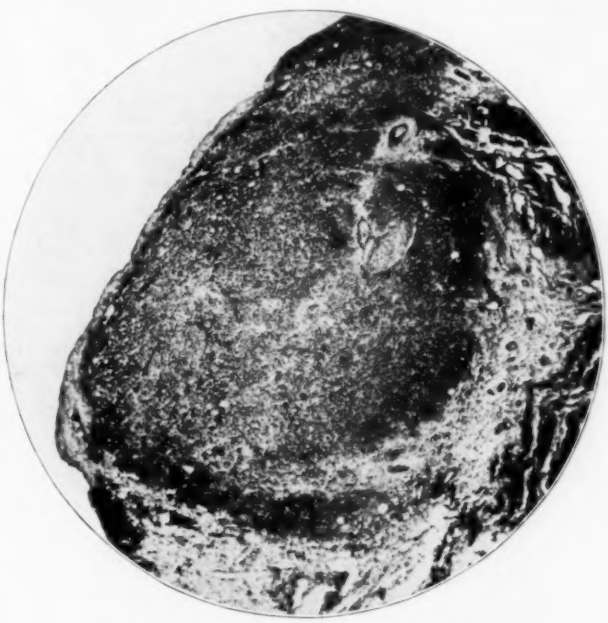

Fig. 3.—The nodule as it appeared in the epicardium.

occasions was bloody. Its specific gravity varied between 1.010 and 1.016. It was odorless and sterile on culture. The cell count showed 795 cells per cubic millimeter, of which the polymorphonuclear cells constituted 13 per cent, the small lymphocytic cells 71 per cent, the endothelial cells 6 per cent and the large mononuclear cells 10 per cent. Some of the fluid was injected intraperitoneally into a guinea-pig, but evidence of tuberculosis could not be found three months later. The Wassermann reaction of the pleural fluid was strongly positive.

Repeated examinations of the patient's sputum for tubercle bacilli, spirilla and fungi revealed none. The chemical analysis of the blood showed nonprotein nitrogen 37.2 mg., uric acid 6.2 mg., creatinine 1 mg. and sugar 101 mg. per hundred cubic centimeters. The Wassermann reaction of the blood was plus 3. The blood pressure was 100 systolic and 80 diastolic. The blood count showed:

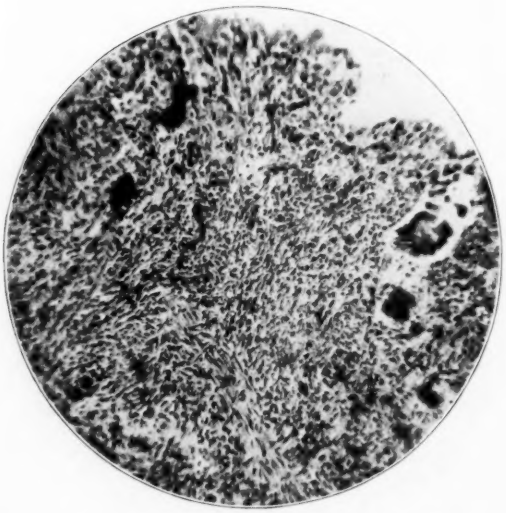

Fig. 4.—The lesion in the intestine, showing disorderly interlacing bundles of spindle cells.

Fig. 5.—The periphery of the intestinal lesion, showing pigment deposit.

hemoglobin content 78 per cent, red cells 5,000,000 and white cells 12,400. The differential count showed: polymorphonuclear cells 58 per cent, large lymphocytic cells 35 per cent, small lymphocytic cells 6 per cent and eosinophilic cells 1 per cent. The urine was acid in reaction. The specific gravity was 1.020. A faint trace of albumin, a few hyaline casts and calcium oxalate crystals were reported present. The patient was treated with neoarsphenamine and bismuth, and later with gold sodium thiosulphate, but without any therapeutic effect on the lesions of the skin. The patient grew progressively weaker and died of bronchopneumonia. During the last eight weeks of his life, he suffered from severe, unexplainable abdominal pains and marked constipation.

Fig. 6.—The intestinal lesion, showing type of cell and newly formed capillaries.

Postmortem Examination.—Lesions similar to those of the skin were found in the epicardium, the bronchial mucosa and the mucosa of the ileum.

In the epicardium, they were situated along the course of the coronary vessels, especially the coronary sinus. The nodules there were elongated, dark red and hard, and when incised resembled an organizing blood clot. The superficial muscle fibers were invaded for a distance of 4 or 5 mm. The bronchial lesion was represented by small hemorrhagic patches. In the intestine, the process was marked by thickening of the wall. The serous surface was mottled red, slightly opaque and lacking in luster. The overlying mucosa showed an ulcer 2 by 4 cm. in diameter, the floor of which was dark red and necrotic and the edges of which were elevated and indurated. There were many of these ulcers along the course of the ileum.

Microscopic Examination.—Low magnification emphasized the nodular character of the process. The cellular arrangement varied. In the centers of some nodules, apparently the younger ones, there were many large endothelial spaces filled with red blood cells and much free hemorrhage. Mononuclear leukocytes, plasma cells and eosinophils might be seen in abundance. Near the periphery were newly formed branching capillaries. The vascular endothelial cells were large and stained deeply, and the lumen was broad. Between the capillaries were a few small mononuclear cells and many large elongated cells, some of which behaved like fibroblasts and some of which resembled the endothelial leukocyte of Mallory. These spindle cells formed bundles, which interlaced in a disorderly manner. At

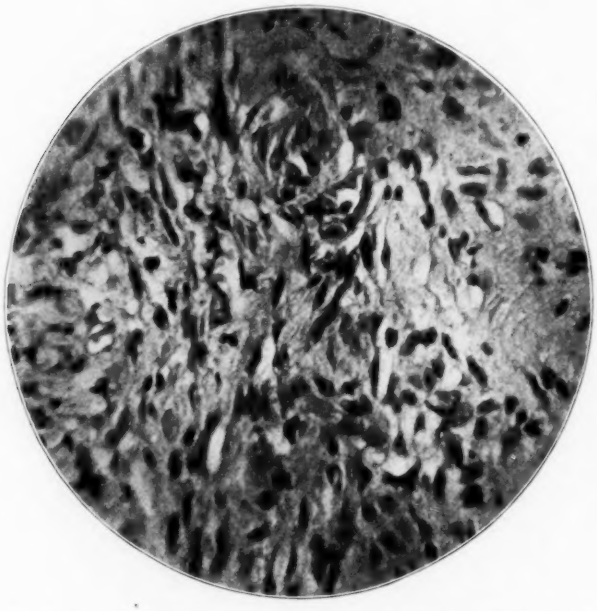

Fig. 7.—A section showing the type of cell and the intercellular hyaline connective tissue.

another stage, the hemorrhagic center was not seen; prominent capillaries embedded in entangled, interlacing bundles of spindle cells formed the entire nodule; the latter sometimes subdivided it into smaller secondary nodules. Large mononuclear leukocytes (so-called epithelioid cells or endothelial leukocytes) lay between the bundles and the capillaries. In the periphery, an abundant brownish pigment was found, most but not all of which became blue when treated with potassium ferrocyanide. At still another stage, hyalinization occurred. It is most peculiar that thick hyaline walls developed even in these newly formed capillaries. The hyaline material was deposited outside the endothelium as a ring or within the lumen, nearly or completely obliterating it. Hyaline material infiltrated, so it seemed, the intercapillary spaces, displacing the many cells seen in other stages. A stage that we take to be final was represented by a homogeneous structure, or

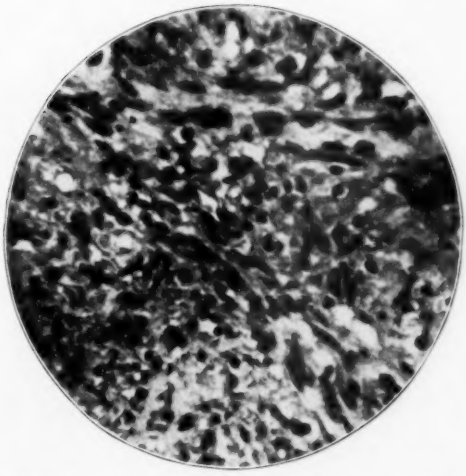

Fig. 8.—The intestinal lesion, showing newly formed capillaries and hemorrhage.

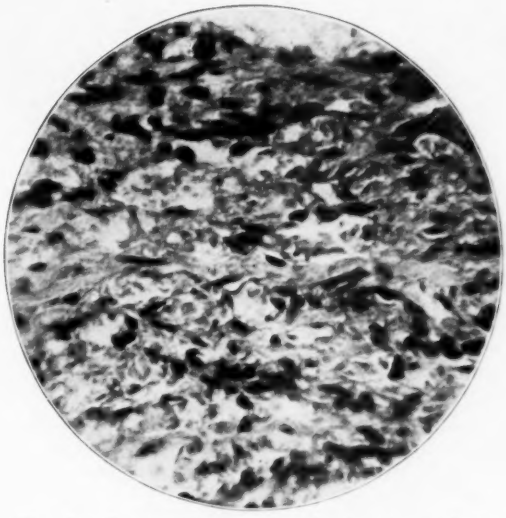

Fig. 9.—The intestinal lesion, showing hemorrhage.

one made up of coarse, wavy fibrils, between which there were spindle cells, much brown pigment and sometimes much hemorrhage.

We are inclined to look on the lesion as progressing in stages in the order in which they have been given, but it is far from certain that such is always the case.

The lesions of the skin showed less hemorrhage, but were, in general, like those of other parts of the body. Those of the pericardium seemed most typical. In the intestine, they seemed to have started in the submucosa and extended into the mucosa, causing ulceration secondarily. The underlying serosa was thickened and hyalinized. Yet, in these sections, the musculature was intact, so that the process in the serosa was not directly a part of the one seen in the submucosa, but

Fig. 10.—The intestinal lesion, showing sclerosis and occlusion of capillaries in the periphery.

probably an older one. It is our opinion that the lesion appeared in the bronchiole extension from an origin in the adventitia of an associated arteriole. The process here was the same as elsewhere.

We noted with interest collections of small mononuclear cells in the sheaths of nerves of the epicardium and in the adventitia of arterioles not the seat of a definite lesion like that described. Similar collections were also found independent of nerves or arterioles, in the heart, lungs, kidneys and liver.

Bacterial cultures of the tissues were not made, but sections stained for bacteria (including the tubercle bacillus) revealed none. Bacteria of many forms were seen in the intestinal ulcer superficially, but not deep in the lesion; therefore, we assumed these to be secondary invaders of a devitalized tissue. Sections were also examined for *Treponema pallidum*, but none was found.

Other lesions found at autopsy and confirmed by microscopic study were bronchopneumonia, chronic aortitis, splenic congestion, fibrosis of the splenic capsule and moderate renal sclerosis.

COMMENT

It is reasonable to assume from our study that neither the existence nor the significance of the syndrome is as yet appreciated by internists. It is not possible to state the frequency with which the syndrome occurs. But from the perusal of the literature and from the observation of patients with this condition at clinics and at dermatologic clinical conferences, it is evident that the malady is not uncommon. The reasons for

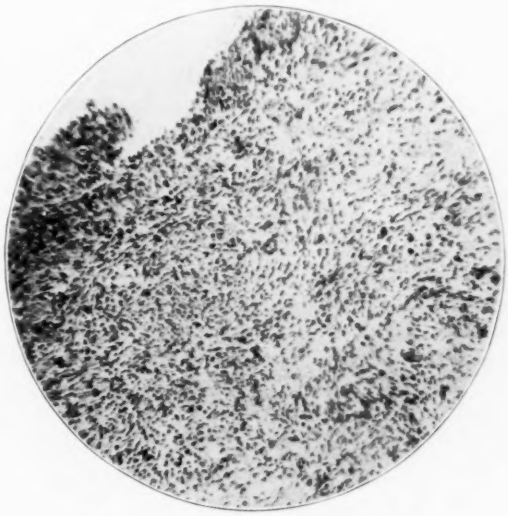

Fig. 11.—The lesion in the bronchus.

the infrequency of reports of patients having systemic lesions are various: We already have had occasion to refer to an instance, and undoubtedly there are many more, in which systemic lesions of Boeck's sarcoid had been confused with tuberculosis. In the past, the cutaneous lesions absorbed all the interest and the systemic lesions were not suspected; consequently, no search was made for them. Then, again, it is not possible, at times, to determine the presence of lesions elsewhere without the aid of a postmortem examination. A good example of this is had in the case of our patient. Incidentally, there is, at the time of writing, a second patient in the hospital with definite sarcoid lesions. The patient's history and the Wassermann reaction of the blood suggest syphilis, but the conditions in the chest are suggestive of chronic tuber-

culosis. Yet repeated examinations of the sputum for tubercle bacilli reveal none. It is clear that Boeck's sarcoid invades organs and tissues; it is the cause of a syndrome that may resemble one of a number of chronic diseases. The resemblance to chronic pulmonary tuberculosis is striking, as illustrated by the patient under observation at this hospital at the time of writing, as well as by the patient reported herein. Clinically, Boeck's sarcoid cannot be mistaken for any other condition, and its presence on the skin should instantly suggest the syndrome in a patient whose chest or abdominal condition cannot answer the requirements of known chronic diseases.

SUMMARY

The lesion described occurs as hard nodules or a group of nodules in the skin, and in the mucous and serous membranes, frequently near or in the adventitia of a small blood vessel. The nodule is characterized grossly by a red or bluish red, which does not disappear on pressure, but which, in time, may fade to a red brown. Studied microscopically, the nodule is found in various stages. At first, it is hemorrhagic and is infiltrated by mononuclear cells. Capillaries appear in the periphery and extend inward followed by spindle cells and large mononuclear leukocytes. The spindle cells form entangled interlacing bundles and with the mononuclear leukocytes and newly formed capillaries occupy the entire nodule. Hyalinization transforms the cellular structure to a relatively acellular homogeneous one containing much iron pigment and a few thick-walled vessels.

Areas of perivascular and perineural mononuclear infiltration and independent collections of mononuclears, as seen in the liver and elsewhere, are manifestations of syphilis, which the positive Wassermann reaction suggests.

If one bears in mind that Boeck's sarcoid is not limited to the skin but may occur in the viscera, the diagnosis of Boeck's sarcoid syndrome must be given consideration as one of the possibilities in a patient who is suffering from a chronic ailment.

CONCLUSION

Boeck's sarcoid is an inflammatory, chronic, infectious granuloma. The rational etiologic attitude to assume toward this condition is that it is caused by syphilis as well as by tuberculosis.

MALIGNANT LESIONS OF THE GALLBLADDER *

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This report is based on a clinical and pathologic study of fifty-six operatively removed specimens of malignant gallbladders. Microscopic sections were made and stained with hematoxylin and eosin; the corresponding case histories were studied and comparisons were made. The series does not comprise the total number of malignant lesions of the gallbladder removed at the Mayo Clinic, but only those specimens available and suitable for study. The records of the pathologic museum show that 14,978 gallbladders removed at operation were sent to the museum between 1910 and 1927, and that 89 of these were malignant.

INCIDENCE

The incidence of malignancy of the gallbladder is commonly given as ranging from 0.5 to 5 per cent. Murphy,[1] in one of his clinics, stated that carcinoma of the gallbladder is a rare disease. W. J. Mayo,[2] in an earlier report on 405 operations performed on the gallbladder and biliary passages for all causes, found that 5 per cent were for malignant disease. Smithies,[3] in a report of twenty-three proved instances of the disease, gave the percentage as 2.3. Erdmann,[4] in a series of 224 cases, found a percentage of 6.7, and observed that the occurrence of malignant lesions of the gallbladder was about 6 per cent of that of all malignant lesions. In his series the number of malignant lesions specified in various organs were: gallbladder fifteen, stomach forty-three, breast sixty-six, colon and sigmoid twenty-eight, rectum and rectosigmoid twenty-nine, cecum twelve, and not specially classified seventy-nine (including malignant lesions of the uterus, kidney, tongue, liver and thyroid gland). MacCarty,[5] in 1919, published a survey of 4,908

* Submitted for publication, June 21, 1929.

1. Murphy, J. B.: Carcinoma of Cholelithic Gallbladder, Exploratory Celiotomy, Surg. Clin. **5**:427, 1916.

2. Mayo, W. J.: Malignant Disease Involving the Gallbladder, Med. News **81**:1105, 1902.

3. Smithies, F.: Primary Carcinoma of the Gallbladder: An Analysis of Twenty-Three Proved Instances of the Disease, Am. J. M. Sc. **157**:67, 1919.

4. Erdmann, J. F.: Incidence of Malignancy in Disease of the Gallbladder, Am. J. Obst. **80**:618, 1919.

5. MacCarty, W. C.: The Frequency of the "Strawberry" Gallbladders, Ann. Surg. **69**:131, 1919.

gallbladders removed at operation; in that series there were 24 cases of carcinoma, or about 0.5 per cent.

At the Mayo Clinic the relative frequency of malignancy of the gallbladder has diminished from an average of about 5 per cent in earlier years to about 0.5 per cent in later years. In 1910 there were 4 carcinomas in 165 cases in which cholecystectomy was performed, and in 1928 there were 5 carcinomas in 1,094 cases; the difference in percentage is undoubtedly due to the fact that diseased gallbladders are now removed earlier.

AGE AND SEX

The ages of the patients having malignant lesions of the gallbladder varied from 39 to 77 years. Carcinoma of the gallbladder is extremely rare before the age of 30 years. It is practically unheard of in the twenties, but Proescher [6] reported malignancy of the gallbladder in the case of a man aged 22. Although malignancy of the gallbladder may occur at any time in middle age, it manifests itself chiefly in the fifth and sixth decades, 74 per cent occurring between the ages of 50 and 60. Given in half decades, there was one patient between 35 and 40 years of age, one between 40 and 45, four between 45 and 50, twelve between 50 and 55, fifteen between 55 and 60, thirteen between 60 and 65, five between 65 and 70, two between 70 and 75, and three between 75 and 80.

It is commonly reported that women are affected with malignant disease of the gallbladder three times as commonly as men. Siegert [7] found seventy-nine women to fourteen men. W. J. Mayo found about the same proportion. Erdmann's cases were all those of women. In this series there were forty-four women and twelve men, supporting the common contention of the 3:1 proportion. All but five of the women had been pregnant one or more times.

CLINICAL DATA

It is commonly believed that the symptoms of malignancy of the gallbladder are mostly silent, being chiefly those of the milder types of dyspepsia of the gallbladder. Although this is true in some instances, most patients have a history which is at least suggestive. Patients with malignant lesions of the gallbladder may roughly be placed in three groups. The first group, comprising about 70 per cent, has a history of repeated attacks of colic of the gallbladder over a period of from several to many years, followed by a change in symptoms designating the malignant phase, which is usually of from three to six months'

6. Proescher, Frederick: A Remarkable Case of Carcinoma of the Gallbladder in a Man Twenty-Two Years Old, J. A. M. A. **48**:481 (Feb. 9) 1907.

7. Siegert, quoted by Mayo (footnote 2).

duration. This terminal stage of disease of the gallbladder is characterized by constant pain in the epigastrium or right upper quadrant of the abdomen, vomiting, profound anorexia, weakness, and progressive loss of weight of from 15 to 30 pounds (6.8 to 13.6 Kg.) in from three to six months. The second group, comprising about 22 per cent, has symptoms of an apparently harmless condition of the gallbladder, such as intolerance for food, gastric distress after eating, belching, constipation, sour eructations and a minimal amount of pain and tenderness over the area of the gallbladder, not associated with weakness, loss of weight or loss of appetite. The third group, or about 9 per cent, has apparently not been conscious of any disease of the gallbladder prior to a terminal malignant stage, in which there is a fairly sudden onset of pain, progressive loss of weight and marked weakness and anorexia.

Jaundice may be present, depending on encroachment on the biliary duct system or extensive involvement of the liver. Thirteen of the fifty-six patients had jaundice at the time of the examination.

There is usually a fair degree of tenderness in the area of the gallbladder. A mass was palpable in twenty-nine cases (55 per cent), and seven of the patients had felt the tumor themselves.

The gastric acids were available in twenty-three cases. There were only four in which achlorhydria was present; in these cases the average total acidity was 15. In the remaining nineteen cases the average hydrochloric acid was 32, and the average total acidity was 48.

The blood picture in cases of malignant disease of the gallbladder is not that frequently found in cases of malignant disease in other parts of the body, in that anemia is not associated. Only five of the patients in the series reported here had a hemoglobin of less than 70 per cent, and none had a hemoglobin of less than 60 per cent. The average hemoglobin for the entire series was 73 per cent (Dare) which is considered within normal limits at the clinic.

Metastasis may take place in the liver, the adjacent lymph nodes, or the extrahepatic biliary duct system. In 35 per cent of the cases there was extension into the liver and in five of these there was involvement of the regional lymph nodes. Metastasis to regional lymph nodes alone was found in eight cases. In five there was extension into the biliary passages and in one of these the lymph nodes were affected.

Stones were found to be an almost constantly associated factor. In Deaver's [8] experience calculi were found in 89 per cent of cases of carcinoma of the gallbladder. Courvoisier [9] found that in seventy-four of eighty-four cases of malignant disease of the gallbladder, stones

8. Deaver, J. B.: Carcinoma of the Gallbladder, Am. J. Surg. **38**:105, 1924.
9. Courvoisier, quoted by Mayo (footnote 2).

Fig. 1.—Adenocarcinoma of the gallbladder.

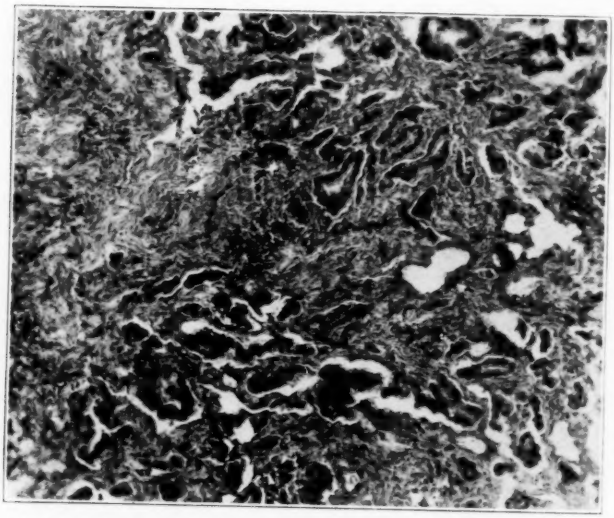

Fig. 2.—Adenocarcinoma of the gallbladder with acini containing columnar epithelial cells.

were present. Siegert stated that in cases in which the neoplasm was primary, stones were present in 95 per cent, and in cases in which neoplasm was secondary, stones were present in 15 per cent. In the present series, stones were present in fifty-three cases (94 per cent).

Cholecystectomy only was performed in twenty-nine cases and partial cholecystectomy only in five cases. Cholecystectomy with choledochostomy for relief of obstruction of the common duct was performed in four cases, and in one of these a portion of the common duct was likewise resected. Cholecystostomy only was performed in eight cases. In one case, gastro-enterostomy along with cholecystectomy was necessary because of pyloric obstruction. In seven cases the only surgical

Fig. 3.—Gross appearance; squamous cell epithelioma of the gallbladder.

procedure was exploratory operation and removal of a specimen for diagnosis. Choledochostomy was performed in one case and jejunostomy in one.

POSTOPERATIVE LONGEVITY

No record of longevity was available in nine cases. Webber,[10] in a recent article, graded many of these specimens according to the method of Broders [11] and gave the corresponding duration of life in that paper. Therefore an attempt was not made in this report to compare the grade

10. Webber, I. M.: Grades of Malignancy in Primary Carcinoma of Gallbladder, Surg. Gynec. Obst. **44**:756, 1927.

11. Broders, A. C.: Carcinoma: Grading and Practical Application, Arch. Path. **2**:376 (Sept.) 1926.

Fig. 4.—Squamous cell epithelioma of the gallbladder containing epithelial pearls.

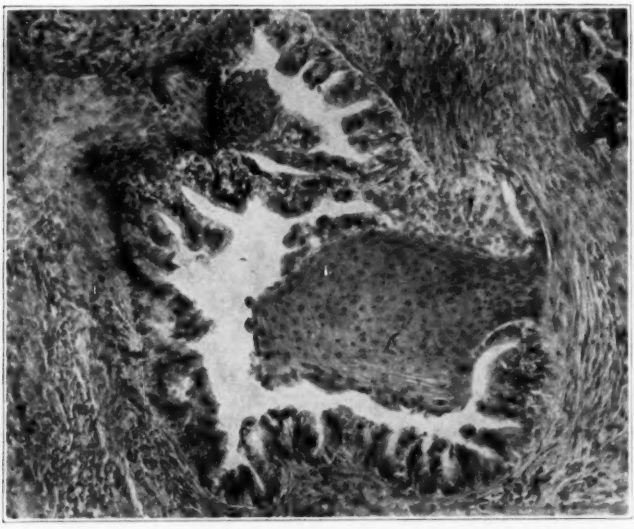

Fig. 5.—Squamous cell epithelium and adenocarcinoma in the same alveolus.

of malignancy with expectancy of life. Twelve patients lived one month or less; seven lived two months; three lived four months; three lived five months; two lived six months; three lived seven months; one lived eight months; one lived nine months; one lived less than one year, but the exact date of death was not given; three lived one year; one lived thirteen months; one lived fourteen months; one lived somewhat less than three years; three lived four years, and in one of these cases the family physician reported carcinoma of the liver at necropsy, although this was probably a slow extension from the old malignant lesion of the gallbladder. One patient lived seven years and one lived eight years. Three patients were alive after fifteen months, eight years, and fourteen years, respectively.

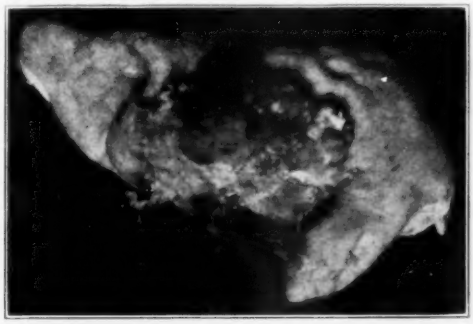

Fig. 6.—Papillary adenocarcinoma of the gallbladder.

PATHOLOGY

Microscopic sections were made and examined, and graded by Broders according to the method previously described by him.

The types of malignancy of the gallbladder in this series are: adenocarcinoma, squamous cell epithelioma, papillary carcinoma and sarcoma.

Adenocarcinoma occurred most commonly. These types consist of branching acini of round or oval cylindric cells; some of these surround a central lumen, and others completely obliterate the lumen. There were forty-nine belonging to the adenocarcinoma group (figs. 1 and 2). The malignancy in these cases was graded 1 in four cases, 2 in twenty cases, 3 in eleven cases and 4 in fourteen cases.

There were three cases of squamous cell epithelioma (figs. 3 and 4). These growths contained squamous cells, intracellular fibers and horny cell nests. This type of tumor is rare. Nicholson,[12] in 1919, reported

12. Nicholson, G. W.: Three Cases of Squamous-Celled Carcinoma of the Gallbladder, J. Path. & Bact. **13**:41, 1909.

three cases of squamous cell epithelioma of the gallbladder, and sixtee. others that he reviewed from the literature. Various theories have been advanced as to the possible causes of this condition, and two that have been suggested apparently deserve serious consideration: 1. It is due to misplaced embryonic tissue probably from an esophageal anlage. 2. It is due to metaplasia; this hypothesis is the more likely.

Metaplasia has been variously defined [13] as the transition of one tissue into another of a related kind, or as the formation of different tissues from a common parent cell. It has been noted in various organs, including the skin, gallbladder, stomach, breast and uterus. Just what

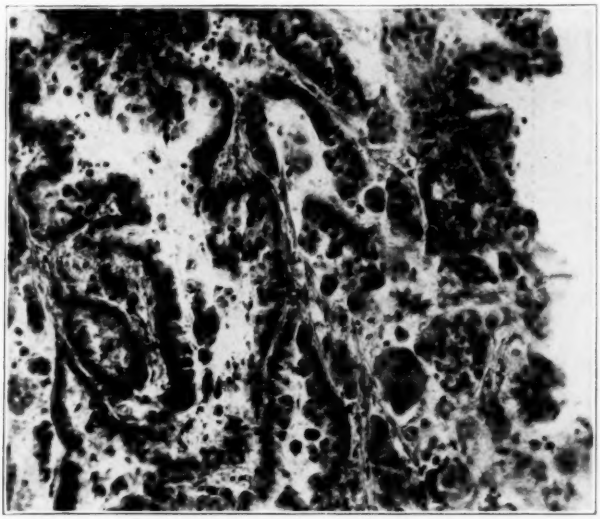

Fig. 7.—Papillary adenocarcinoma of the gallbladder, illustrating the papillary character of the tumor.

initiates the change of one tissue to another of a related kind is not known, but apparently chronic inflammation or irritation is necessary for the process. Futterer [14] has been able to produce metaplasia in the pyloric end of the stomach of rabbits by long-continued irritation. Normally, squamous epithelium does not exist in the gallbladder or in any of the adjacent organs, and so it is only by assuming that these tumors arose partly because of the change of the tissue by metaplasia

13. Caylor, H. D.: Practical Considerations of Metaplasia in Neoplastic Diseases, J. Lab. & Clin. Med. **13**:714, 1928.

14. Futterer, G.: Ueber experemintelle Erzeugung von Magengeschwüren und über Schleimhautwucherungen an deren Randern, Festschr. f. G. E. von Rindfleisch, 1907, p. 89.

that their origin can be explained.[15] Of such epitheliomas in this series there was one each of grade 1, 2 and 3, according to Broders' system of grading. There were two other specimens, examples of metaplasia, which contained both adenocarcinoma and squamous cell epithelioma graded 2. In one of these tumors (fig. 5), adenocarcinoma formed a portion of a single acinus, and squamous cell epithelioma formed the remainder of the same alveolus.

There was one case of papillary adenocarcinoma graded 3 (figs. 6 and 7). The relationship between papilloma and papillary carcinoma is problematic. About 10 per cent of all gallbladders have one or more

Fig. 8.—Lymphosarcoma of the gallbladder.

papillomas, yet papillary carcinoma is relatively rare. Hruska[16] and Ringel,[17] however, both reported malignant degeneration in the papillomas.

There was one case of lymphosarcoma of the gallbladder, associated with stones (figs. 8 and 9). The patient was a woman aged 41. In 1914, Iwasaki[18] reported a case of his own and at that time found

15. Lubarsch, Otto: Die Metaplasiefrage und ihre Bedeutung für die Geschwulstlehre, Arb. a. d. path. anat. Abt. d. k. hyg. Inst. zu Posen, 1901, p. 205.

16. Hruska: Einen Fall von krebsiger Umwandlung eines Papilloms der Gallenblase, Wien. klin. Wchnschr. **29**:1263, 1916.

17. Ringel: Ueber Papillom der Gallenblase, Arch. f. klin. Chir. **59**:161, 1899.

18. Iwasaki, K.: Ueber das primäre Sarkom der Gallenblase, Arch. f. klin. Chir. **104**:84, 1914.

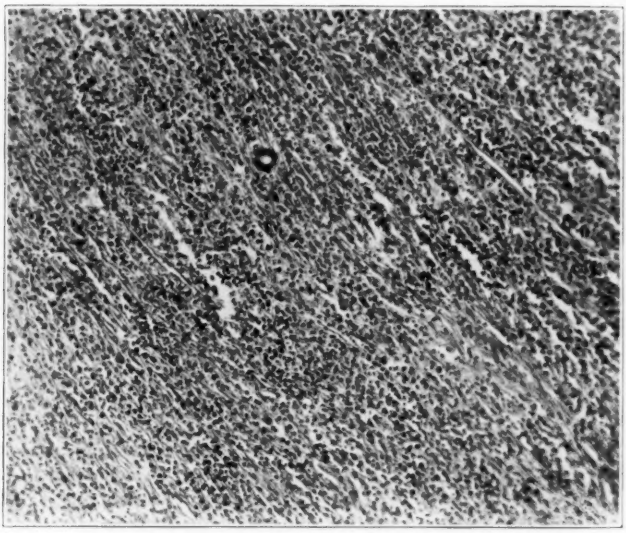

Fig. 9.—Lymphosarcoma of the gallbladder (low power magnification).

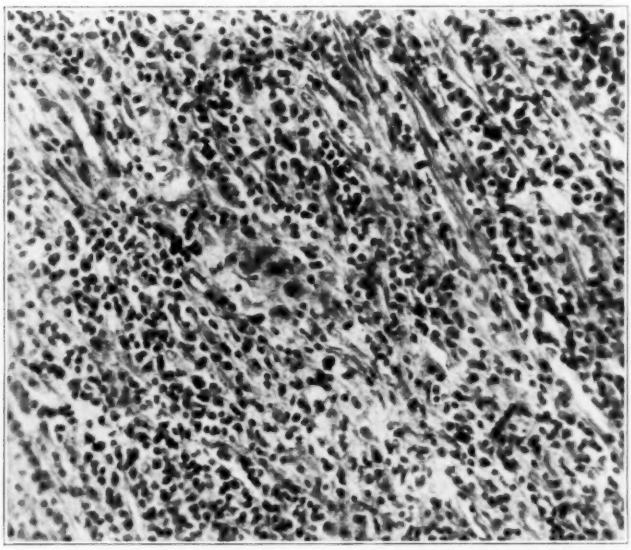

Fig. 10.—Lymphosarcoma of the gallbladder, illustrating more intimate details of the tumor cells.

only eight other cases in the literature. Carson and Smith [19] reported a case in 1915, and in 1921 Goldstein [20] was able to find only sixteen cases of primary sarcoma of the gallbladder in the literature.

SUMMARY

A clinical and pathologic study has been made of fifty-six cases of malignancy of the gallbladder.

The incidence of malignancy of the gallbladder is about 0.5 per cent. It rarely occurs before the age of 50, and women are affected about three times as commonly as men.

Although the symptoms of malignancy of the gallbladder are not definite, about 70 per cent of patients have a long history of repeated gallbladder attacks, followed by a short phase characterized by constant pain, anorexia, vomiting and progressive weakness and loss of weight.

There is almost never an associated anemia in malignancy of the gallbladder. In about a sixth of the cases there is achlorhydria, and in the remaining cases the average free hydrochloric acidity is 32, and the average total acidity, 48.

Stones are an almost constantly associated condition in cases of malignant disease of the gallbladder, 94 per cent of gallbladders having calculi.

The types of malignancy of the gallbladder are adenocarcinoma, squamous cell epithelioma and sarcoma. Adenocarcinoma occurs most commonly. Squamous cell epithelioma occurs as a process of metaplasia, probably from long-continued irritation.

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19. Carson, N. B., and Smith, G. M.: Primary Sarcoma of the Gallbladder, Ann. Surg. **62**:688, 1915.

20. Goldstein, H. I.: Primary Sarcoma of the Gallbladder, Am. J. Surg. **35**: 351, 1921.

CARCINOMA OF THE RENAL CORTEX WITH FACTORS BEARING ON PROGNOSIS *

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Carcinoma of the renal cortex presents a complex pathologic problem, so complex that since Grawitz,[1] in 1884, gave the first accurate description of the condition and called attention to the relation of the structure of renal carcinoma to that of the suprarenal gland, observers have constantly been attempting to name the entire group by some embryologic, histologic or other descriptive term.

Birch-Hirschfield termed the tumor described by Grawitz "hypernephroma." Adami,[2] on a basis of embryologic development, suggested the term "mesothelioma." Sudeck[3] took exception to associating the tumor described by Grawitz with suprarenal rests, favoring their association with renal adenoma. Stoerk[4] supported Sudeck's views and advanced the hypothesis that hypernephroma might arise from proliferations of the adult secreting epithelium of the convoluted tubules. Wilson and Willis[5] concluded that there was almost no evidence, embryologic or histologic, in support of Grawitz' hypothesis that so-called hypernephromas have their origin in suprarenal rests, feeling rather that the evidence at hand favored the hypothesis that hypernephromas originate from islands of nephrogenic tissue (primitive renal blastoma). More recently the comprehensive term, nephroma, was suggested to include tumors originating in the kidney. At the present time, however, the majority of pathologists are inclined to look on all epithelial tumors of the renal cortex as carcinoma. MacCarty,[6] Bro-

* Submitted for publication, June 19, 1929.

1. Grawitz, Paul: Die Entstehung von Nierentumoren aus Nebennierengewebe, Arch. f. klin. Chir. **30**:824, 1884.

2. Adami, J. G.: The Principles of Pathology, ed. 1, Philadelphia, Lea & Febiger, 1909, p. 768; ed. 2, 1910, p. 807.

3. Sudeck, Paul: Ueber die Structur der Nierenadenome. Ihre Stellung zu den Strumae suprarenals aberratae (Grawitz), Arch. f. path. Anat. **133**:405, 1893.

4. Stoerk, Oskar: Zur Histogenese der Grawitzschen Nierengeschwülste, Beitr. z. path. Anat. u. z. allg. Path. **43**:393, 1908.

5. Wilson, L. B., and Willis, B. C.: A Comparative Study of the Histology of the So-Called Hypernephromata and the Embryology of the Nephridial and Adrenal Tissues, J. M. Research **24**:73, 1911.

6. MacCarty, W. C.: Personal communication.

ders [7] and Robertson [8] classify them as carcinomas, mostly of renal origin, and believe that the various pathologic features represent different degrees of cellular differentiation.

Foulds and Braasch [9] have pointed out that two separate groups of cortical tumors can be demonstrated pathologically and clinically, adenocarcinoma and alveolar carcinoma. Those in the group of adenocarcinoma, or those otherwise known as hypernephroma, are characterized by a higher degree of cellular differentiation than is found in those of the group of alveolar carcinoma in which there is less cellular differentiation. In alveolar carcinoma, in many instances, there are solid cords, without lumens, composed of granular or clear cells. The clinical course of patients with adenocarcinoma is distinct from that of patients with alveolar carcinoma. Possibly some of the discrepancies noted in data concerning such tumors are due to the combination in the same tumor of features of adenocarcinoma and of alveolar carcinoma.

MATERIAL

This study comprises a series of 367 cases of carcinoma of the kidney seen at the Mayo Clinic from Jan. 1, 1901, to Jan. 1, 1928. It includes 225 cases reported by Hunt and Hager [10] in a recent review of 271 cases of malignant neoplasm, seen at the Mayo Clinic between Jan. 1, 1918, and Jan. 1, 1928. Of the 312 patients who underwent nephrectomy, 283 have been traced. Of the fifty-five patients who were submitted to exploration, only forty-seven have been traced. In all the patients traced, the age, sex, symptoms, pathologic features, operative procedure, supplementary treatment such as that by roentgen ray and radium, metastasis, and associated infection have been considered in order to determine their bearing on the postoperative length of life. In this paper we shall refer to the entire group under the name of renal carcinoma. We shall designate the less malignant group, generally called hypernephroma, as adenocarcinoma, and the more malignant group as alveolar carcinoma.

PATHOLOGY

Adenocarcinomas of the kidney are frequently associated with tortuous, dilated superficial veins; these are often ruptured and cause troublesome bleeding during nephrectomy. In fifty-one of those patients who were traced, the renal carcinomas were confined to the upper pole; in sixty, they were limited to the lower pole; in thirty-nine, the

7. Broders, A. C.: Personal communication.

8. Robertson, H. E.: Personal communication.

9. Foulds, G. S., and Braasch, W. F.: Postoperative Results of Nephrolithiasis, J. Urol. **11**:525, 1924.

10. Hunt, V. C., and Hager, B. H.: A Review of 271 Cases of Malignant Renal Neoplasms, S. Clin. N. Amer. **9**:149, 1929.

lesions were in the midrenal region; in ten, the entire kidney was involved, and in 123 the involvement was in combinations of the regions mentioned. In 104 patients, the renal capsule was broken through by the carcinoma, and the perirenal tissues were involved. Extension had occurred into the renal veins (fig. 1) in fifty-one cases. Metastasis was observed in ninety-eight instances.

In advanced and fatal cases, carcinomas become large, destroying most of the kidney and undergoing necrosis and hemorrhagic and cystic softening. Extension occurs by continuity through the kidney. The renal pelvis is often encroached on, or the ureteropelvic juncture is obstructed and hydronephrosis results.

Fig. 1.—Carcinoma of the kidney, graded 4, with extension into the pelvis and veins; associated hydronephrosis; destruction of practically all of the renal substance. A woman, aged 52 years, had had hematuria ten years and again five months before operation. She first noticed tumor in the right upper quadrant of the abdomen about five months before operation. Nephrectomy was performed Oct. 15, 1925. The patient is now living and well.

In some specimens the histologic structure presents definite tubules closely resembling a renal tubule and lined by dark, granular cells; in others, the structure is the same, but the cells are clear. In the majority of these carcinomas there is a cystic papillary structure (figs. 2 and 3) without distinct tubules and with clear (fig. 4) or granular cells. In other carcinomas the structure is one of solid cords (alveolar) without lumens and with granular or clear cells. Occasionally the microscopic picture consists of darkly staining cells arranged loosely, like a round cell sarcoma. Two or more of these types of tissue are

Fig. 2.—Typical structure of papillary adenocarcinoma; × 60.

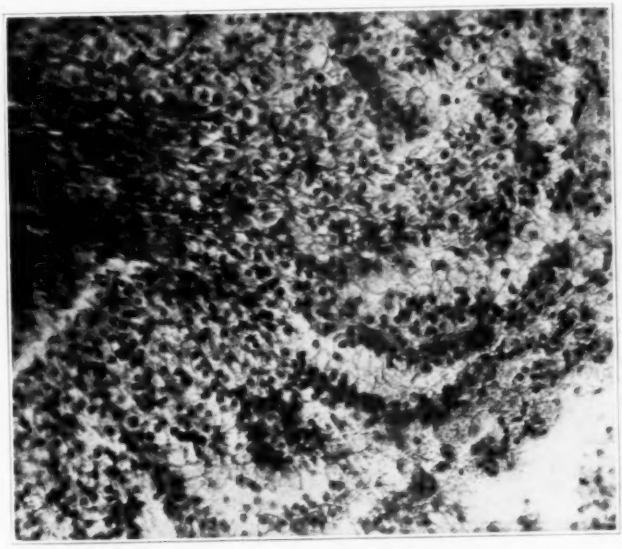

Fig. 3.—Papillary adenocarcinoma; × 120.

often presented in different parts of the same carcinoma. It is possible that a few of the alveolar carcinomas may arise from suprarenal rests, but there is no convincing evidence of this origin. Alveolar carcinomas are less common than carcinomas of the papillary type. In the patients who underwent nephrectomy or exploration and who were traced, the proportion of alveolar carcinoma to adenocarcinoma was 43:287.

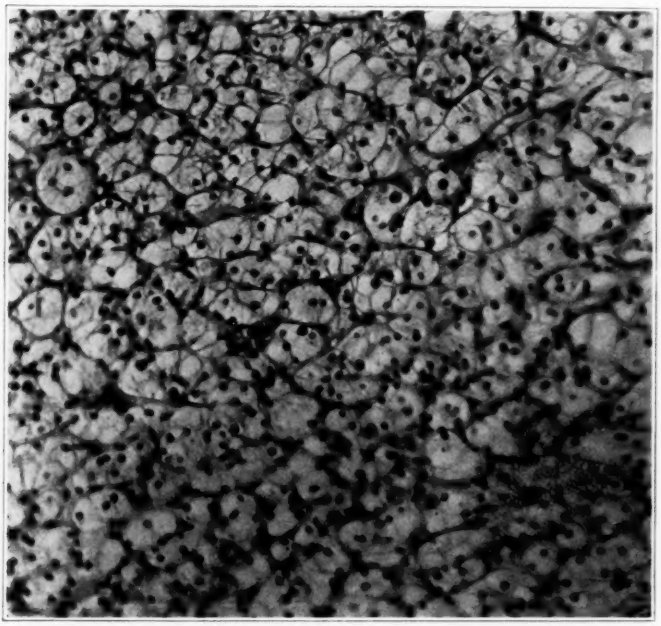

Fig. 4.—Clear, undifferentiated, foamy appearing cells, usually recognized as characteristic of hypernephroma; × 200. According to terminology in this paper the tumor would be called a clear-celled papillary carcinoma. There was almost complete destruction of the renal substance in this case. The patient lived four and a half years after operation.

The lesion involved the right kidney in 169 cases (46.04 per cent) of the series, and the left kidney in 196 cases (53.40 per cent). In two instances the side involved was not stated. Our records show that twenty-six of the 283 patients who underwent nephrectomy and who were traced lived ten years or more; in fifteen of these, the carcinoma involved the right kidney (57.67 per cent), and in eleven the left kidney (42.31 per cent).

RELATION OF AGE TO ONSET OF SYMPTOMS AND POSTOPERATIVE LENGTH OF LIFE IN RENAL CARCINOMA

In this series of 367 patients, the average age was 51.76 years. The age at which the first symptom appeared and the time that elapsed before surgical operation was undertaken had a direct bearing on longevity. One hundred sixty-one patients had the first symptom before the age of 50; in 203, the first symptom appeared after the age of 50, and in three the age was not recorded. In 63 per cent the first symptom occurred between the ages of 40 and 60 years, whereas in 37 per cent it appeared between the ages of 50 and 60 years.

In the group of patients who underwent nephrectomy, those who were living Jan. 1, 1929, had acquired symptoms earlier in life and had come to operation earlier than those who died. In 192 patients who underwent nephrectomy and who are dead, the average age at which the first symptom appeared was 50.56 years; the average age at operation was 52 years and 6 months, and the average duration of postoperative life was 28 months. In ninety-one patients who underwent nephrectomy and who still are living, the average age at which the first symptom appeared was 47.01 years, the average age at operation was 50.47 years and the average duration of postoperative life thus far is 80 months (6.65 years).

In the group of forty-seven patients who underwent exploration and who were traced, forty-five are dead. In these the average age at which the first symptom occurred corresponds with the average age at onset in the group in which nephrectomy was done, that is, 50.84 years. However, a long period elapsed between the time of appearance of the first symptom and the time when these patients came to operation. The average age at operation was 53.11 years. The average duration of postoperative life was 1.72 years. In the two patients living at present the symptoms appeared earlier, at the average age of 35 years and 6 months. Here again, the time when the patients came to operation was delayed; the average age at operation was 41 years. The patients have lived an average postoperative life of 29.5 months. In the cases in which exploration alone was possible, a surgical procedure was not undertaken as soon after the onset of symptoms as in the group in which nephrectomy was done.

RELATION OF SEX TO POSTOPERATIVE LENGTH OF LIFE IN RENAL CARCINOMA

Of the 367 patients, 116 were women, and their average age was 50.45 years; 251 were men, and their average age was 52.36 years.

Of the 283 patients who underwent nephrectomy and who were traced, 191 (67 per cent) were men. Of these, 132 are dead; their average postoperative life was 29.12 months. Fifty-nine men are living

and have thus far lived 81.11 months. Ninety-two (32 per cent) of the patients who underwent nephrectomy were women. Sixty are dead, having lived an average postoperative life of 26.48 months. Thirty-two of these ninety-two patients are living and have had an average postoperative life of 79.68 months. The average duration of symptoms before operation in the 191 men was 28.14 months and in the ninety-two women, 26.64 months. The average duration of symptoms and the average postoperative duration of life, both of patients who are dead and of patients who still are living, are less for women than for men. This suggests that possibly renal carcinoma runs a more rapid course in women.

Of the forty-seven patients who underwent exploration and who have been traced, thirty-eight (80 per cent) were men, of whom thirty-six are dead after an average postoperative life of 22.38 months. The two others have been living now for an average postoperative life of 29.05 months. Nine of these patients (19 per cent) were women. Of these, all are dead, after an average postoperative life of 11.41 months. In this group of forty-seven patients who were subjected to exploration only and who have been traced, the average duration of symptoms before operation for the men was 35 months, and for the women, 9.5 months. From these data it will be noted that in the group of patients who underwent nephrectomy and in the patients who were submitted to exploration, the average duration of symptoms and the average length of postoperative life were much less for women than for men. That the average duration of symptoms is less for women may be explained by their noting symptoms and receiving surgical attention sooner than men; that in spite of this, they should have a shorter average postoperative life than men, again suggests that in women the malignant process may possibly run a more rapid course. In the two sexes, the relation of exploration to nephrectomy can be expressed approximately by the following ratios: men, one operation of exploration to five of nephrectomy, and women, one of exploration to ten of nephrectomy. That the proportion of inoperable carcinoma is less in women than it is in men is probably due again to their seeking surgical assistance before the malignant process became locally extensive.

RELATION OF THE DURATION OF SYMPTOMS BEFORE OPERATION TO POSTOPERATIVE LENGTH OF LIFE IN ADENOCARCINOMA AND ALVEOLAR CARCINOMA

The average duration of symptoms before operation was longer in patients subjected to nephrectomy for adenocarcinoma than in those in whom nephrectomy was done for alveolar carcinoma. In the 192 patients on whom nephrectomy was performed, and who died subse-

quently, the average duration of symptoms before operation was 21.73 months for those who had adenocarcinoma and 17.43 months for the corresponding group with alveolar carcinoma. In the ninety-one patients on whom nephrectomy was performed and who still are living, the average duration of symptoms was 40.97 months for the group with adenocarcinoma and 32.5 months for the corresponding group of patients with alveolar carcinoma. From these data it will be seen that in the patients on whom nephrectomy was possible, symptoms were present for a longer time in the group with adenocarcinoma than in the group with alveolar carcinoma.

In forty-seven patients who were traced, the extent of the pathologic process permitted only of an exploration. The average duration of symptoms was much longer in these patients than for those in the group in which nephrectomy was done; this stresses the importance of earlier operation after the advent of symptoms, if nephrectomy is to be possible. In the patients now dead who were submitted for exploration and whose conditions were diagnosed as alveolar carcinoma, the average duration of symptoms was 41.5 months; this is twenty-four months more than the average duration of symptoms in the group with alveolar carcinoma in whom nephrectomy was possible. In those patients who have died in whose cases the diagnosis was adenocarcinoma and exploration alone was possible, the average duration of symptoms was 25.37 months. This is an average of four months longer than the average duration of symptoms in the group with adenocarcinoma in whom nephrectomy was performed.

In the deceased patients who were subjected to exploration and whose conditions were diagnosed as adenocarcinoma, the average postoperative length of life was 21.72 months, whereas in those patients whose conditions were diagnosed as alveolar carcinoma, the average postoperative length of life was 15.85 months.

Of the forty-seven patients who were submitted to exploration and who have been traced, only two are living. In both of these the diagnosis was adenocarcinoma. The average duration of symptoms was 62.5 months and the average postoperative length of life thus far has been 29.5 months. It may be seen from these data that the postoperative course of patients with alveolar carcinoma tends to a more rapidly fatal issue than that of the patients with adenocarcinoma.

FREQUENCY OF SYMPTOMS

Pain was present at some time as a symptom in 307 of the 367 cases (83.65 per cent). Hematuria occurred at some time in 253 cases (68.93 per cent). A tumor was noted in 291 cases (79.29 per cent) Weakness occurred in twenty-nine cases (7.90 per cent). There was absence of

a history of urinary disorder in eight cases (2.17 per cent) and absence of a history of illness in two (0.54 per cent).

TUMOR

The presence of a tumor was noted by patients in fifty-one (13.89 per cent) of the 367 cases; however, a tumor was demonstrated on general examination in 291 of the cases (72.29 per cent). The following data emphasize that as the tumor becomes large enough to be palpable and finally becomes fixed, the mortality rate is increased. Death occurred in thirty-three of sixty-five cases in which a mass was not palpable and in seventeen of thirty cases in which a mass was palpable and in which mention was not made of mobility or fixation. In ninety of the cases a movable mass was recorded; sixty-one of the patients are dead, and twenty-nine are living. In nine cases the mass was definitely recorded as fixed; in eight of these death occurred. The relation of a large mass to mortality is well demonstrated in the forty-seven cases in which exploration only was carried out, and which were traced; a fixed, and in many cases an infiltrating, tumor was noted in forty-four cases. Death has occurred in forty-two of these forty-four cases.

THE SITUATION OF THE CARCINOMA IN THE KIDNEY IN RELATION TO MORTALITY AND POSTOPERATIVE LENGTH OF LIFE

The carcinoma was situated in the upper pole of the kidney in fifty-one instances, in the lower pole in sixty instances, and it occupied the midrenal region (figs. 5 and 6) in thirty-nine instances. In ten instances, the entire kidney was involved. The involvement was not well defined in 123 kidneys. Sixty-six per cent of the patients in whom the involvement was noted in the upper pole of the kidney are dead; 64 per cent of those in whom the growth was in the lower pole also are dead as well as 55 per cent of those in whom the midrenal region was involved.

The patients who still are living, in whom the upper pole of the kidney was involved, have lived a longer average postoperative life than those in whom involvement of the lower pole and midrenal region was noted. The average postoperative length of life in patients still living is 129.46 months for those patients in whom the upper pole of the kidney was involved, as compared with 83.30 months for those with involvement of the lower pole of the kidney, and 76.92 months for those with involvement of the midrenal region. In the patients who died the relation of the situation of the tumor to the postoperative length of life is not so striking. The average postoperative length of life is 40.44 months for those patients in whom the upper pole of the kidney was involved, as compared with 38.09 months for those with involvement of the lower pole of the kidney, and with 39.05 months for those with

involvement of the midrenal region. Tumors of the lower pole of the kidney may interfere with renal drainage, favoring the development of a variable degree of hydronephrosis and infection.

SIZE OF THE CARCINOMA WITH RELATION TO POSTOPERATIVE LENGTH OF LIFE

The size of the carcinoma bears a rather distinct relationship to the mortality rate. In 161 cases in which nephrectomy was performed, the

Fig. 5.—Papillary carcinoma arising from practically the entire convex surface of the kidney. The patient was a man, aged 59 years, who had a mass in the left upper quadrant of the abdomen for two years. He died on the eleventh postoperative day; infection was a contributing cause.

carcinomas were recorded as large; death occurred in 129. In eighty-two cases the carcinomas were moderate in size; fifty of the patients are dead and thirty-two are living. In thirty-six cases the carcinomas were recorded as small; ten of the patients are dead and twenty-six are living. In four cases the size of the tumor was not stated. The patients who had small carcinomas and died lived a much longer postoperative length of life than the patients who had moderate-sized tumors.

Carcinomas were recorded as large in thirty-six of the cases in which exploration was performed. Thirty-five of the patients are dead. In eleven cases in which exploration was carried out, the size of the carcinoma was not stated.

HEMOGLOBIN IN RELATION TO MORTALITY

Irrespective of any other factor, death occurred in 75 per cent of sixty-three cases in which the hemoglobin was less than 60 per cent,

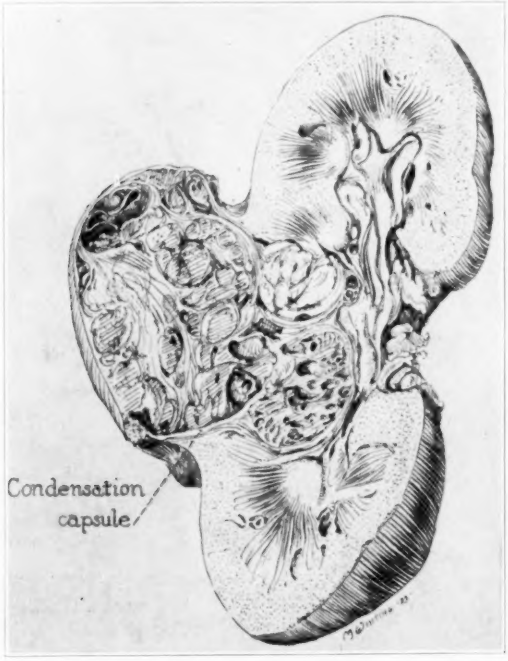

Fig. 6.—Adenocarcinoma involving the middle portion of the left kidney; the lesion is encapsulated. The patient was a man 45 years of age, who had had intermittent attacks of pain and hematuria for five weeks. He is living and well eleven years after nephrectomy.

whereas death occurred in 60 per cent of the 171 cases in which the hemoglobin was recorded as being more than 60 per cent. Further, of 118 cases in which the hemoglobin was less than 70 per cent, death occurred in 76 per cent and in 51 per cent of 116 cases in which the hemoglobin was more than 70 per cent. Thus it will be seen that a direct relationship seems to exist between the hemoglobin at the time of nephrectomy and subsequent mortality.

INVOLVEMENT OF RENAL VEINS

There was extension to the renal veins in fifty-one of the cases in which nephrectomy was done; there have been forty-two deaths, and among these nine deaths in the hospital. In 231 cases, extension to the renal veins was not noted; there were 151 deaths, and among these twenty-one deaths in the hospital. The average postoperative length of life in those patients with involvement of the renal veins who are dead was 24.46 months; the corresponding figure for those patients who were without involvement of the renal veins was 24.37 months. Among the patients who are living, those patients in whom there was involvement of the renal veins had an average postoperative length of life of 72.77 months, whereas the average postoperative length of life for patients still living in whom the renal veins were not involved was 82.09 months. A greater percentage of patients are dead in the group with involvement of the renal veins than in the group without such involvement; metastasis and subsequent pyelophlebitis played major parts as contributory causes of death. Extension to the renal veins greatly increases the difficulty of accurate hemostasis. The veins become rigid and friable and lose their elasticity. After ligation or clamping of the pedicle the contained plug of tissue prevents accurate healing of the incised veins. One patient died on the fourth postoperative day from secondary hemorrhage that followed the removal of clamps from the renal pedicle.

PERIRENAL INVOLVEMENT

In 104 of the cases in which nephrectomy was performed and which were traced, the perirenal tissues were involved, or the capsule was broken through (fig. 7). There have been eighty-four deaths, twelve of which occurred in the hospital; in the other seventy-two cases in which death occurred, the average postoperative life was 17.23 months. In twenty cases of this group, the patients have been living now for an average of 77.2 months. No doubt in some of the cases in which the patients have lived so long the fixation of the tumor noted at the time of operation was the result of inflammatory reaction rather than malignant attachment. Perirenal involvement was not noted in 179 cases. Death occurred in 108 of these, in eighteen of which death occurred in the hospital, and in ninety of which the average postoperative life was 37.22 months. In seventy-one cases in which perirenal involvement was not noted, the average postoperative length of life thus far is 81.15 months. It will be noted here that a much lower mortality rate exists in the cases in which perirenal involvement did not occur. In eighty-four cases the perirenal tissues were involved or the capsule was found broken. In twenty-three of these, there was metastasis, and in thirteen there was local recurrence of the carcinoma. Of the twenty cases in

which the patients are living in which perirenal involvement was noted at operation, metastasis has been reported in only one, and local recurrence in two. This emphasizes the fact that local recurrence and metastasis play major parts as factors in mortality.

Twenty-six patients are dead of the group of twenty-seven of those who underwent exploration and in whom the perirenal tissues were evidently involved or the capsules broken. In this group six instances of metastasis were noted. Metastasis was present in the case of the patient who is still living after exploration in which the perirenal tissue was found to be involved.

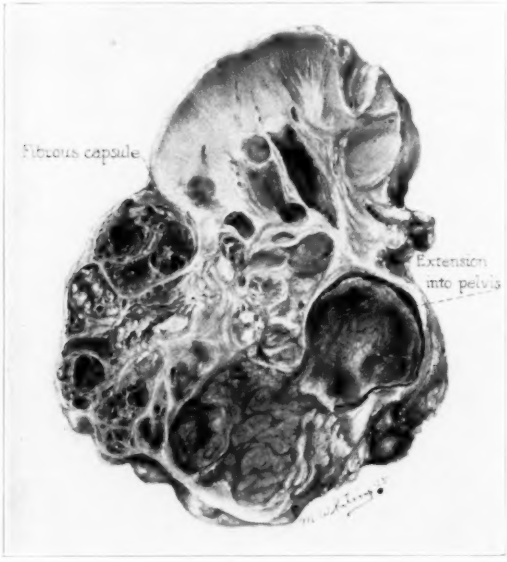

Fig. 7.—Papillary carcinoma 10 by 8 by 6 cm. which had perforated the capsule and projected into the pelvis. The patient was a man, aged 40 years. He gave a history of pain in his back and intermittent hematuria for fourteen months. He lived five years and ten months following right nephrectomy.

The total number of cases in which nephrectomy or exploration was performed and in which the perirenal tissues were found to be involved or the capsules broken was 131 (tables 1 and 2); in thirty-one of these (23.66 per cent) there was metastasis, and in fifteen (11.45 per cent) there was local recurrence. However, in sixty-seven (33.66 per cent) of the 199 cases in which perirenal involvement did not occur or in which the capsule was not broken, there was metastasis, and in thirty-six (18.09 per cent) there was recurrence. The higher percentage of recurrences and metastasis which occurred in the cases without

perirenal involvement would seem to indicate that the gross pathologic condition is not an exact criterion as to whether or not extension has occurred.

OPERATIVE PROCEDURE IN RELATION TO MORTALITY AND POST-OPERATIVE LENGTH OF LIFE

Incision.—In the 283 cases in which nephrectomy was performed and which were traced, the surgical approach was made through a posterior

TABLE 1.—*Record of 312 Patients of Whom 283 Were Traced Who Had Adenocarcinoma or Alveolar Carcinoma of the Kidney and Who Underwent Nephrectomy Between Jan. 1, 1901, and Jan. 1, 1928*

		Deaths (192)			Patients Living (91)	
	Cases	Hospital Deaths	Subsequent Deaths	Average Postoperative Life, Months	Cases	Average Postoperative Life, Months
Males	132	24	108	29.12	50	81.11
Females	60	6	54	26.48	32	79.68
Right	86	15	71	33.59	47	84.61
Left	106	15	91	22.60	44	76.81
Posterior incision	125	18	107	28.88	71	76.88
Anterior incision	63	11	52	25.92	18	100.66
Anterior and posterior incisions	...	..	...	.....	2	33.00
Type of incision not stated	4	1	3	37.00	..	.....
Movable tumor	61	10	51	22.34	29	74.68
Fixed tumor	8	1	7	26.75	1	98.00
Palpable tumor	73	17	56	27.28	16	87.25
Kidney palpable	17	..	17	34.62	13	61.53
No palpable tumor	33	2	31	36.07	32	88.93
Lesion in lower pole	40	4	36	38.09	20	85.30
Lesion in upper pole	36	7	29	40.44	15	129.46
Lesion median in position	23	3	20	39.05	16	76.92
Lesion involved entire kidney	8	3	5	50.20	2	37.00
Situation of lesion indeterminate	85	13	72	14.18	38	62.73
Tumor large	129	24	105	28.37	32	87.53
Tumor moderate sized	50	6	44	25.67	32	78.68
Tumor small	10	..	10	43.20	26	75.96
Size not stated	3	..	3	7.0	1	53.00
Extension into renal vein	42	9	33	26.46	9	72.77
No extension into renal vein	150	21	129	24.37	82	82.09
Perirenal tissue involved or capsule broken	84	12	72	17.23	20	77.20
No involvement	108	18	90	37.22	71	81.15
Forceps on pedicle	25	7	18	22.33	5	85.6
Ligation of pedicle	167	23	144	28.79	86	79.97
Roentgen ray alone	51	..	51	24.37	27	46.03
Roentgen ray and radium	12	..	12	35.09	..	.....
Radium alone	8	1	7	10.57	1	96.00
No radiologic treatment	121	29	92	30.61	63	95.12
Carcinoma	25	5	20	16.86	8	37.00
Hypernephroma	167	25	142	29.67	83	84.77

incision in 196 (69.25 per cent); through an anterior incision in eighty-one (28.62 per cent); and through an anterior and a posterior incision in two cases (70 per cent). In the other four cases (1.41 per cent) the type of incision was not stated.

In the cases in which exploration was performed, posterior incision was used in fourteen cases (29.78 per cent), and an anterior incision, in twenty-nine (61.70 per cent). The type of incision was not stated in four cases (8.51 per cent). In the cases in which exploration was performed, an anterior incision was used in 61.70 per cent, whereas in

cases in which nephrectomy was performed an anterior incision was used in only 28.62 per cent. Because of the greater risk in the anterior incision and also because of technical improvements in the posterior incision, the posterior incision has been used in nearly all cases in the last few years.

Pedicle Controlled by Forceps or Ligature.—In thirty cases, nearly 10 per cent of the total number in which nephrectomy was performed, it was deemed advisable to allow forceps to remain on the vascular pedicle

TABLE 2.—*Record of Fifty-Five Patients, of Whom Forty-Seven Were Traced, Who Had Adenocarcinoma or Alveolar Carcinoma of the Kidney and Who Underwent Exploration Between Jan. 1, 1901, and Jan. 1, 1928*

	Deaths (45)				Patients Living (2)	
	Cases	Hospital Deaths	Subsequent Deaths	Average Postoperative Life, Months	Cases	Average Postoperative Life, Months
Males	36	4	32	22.38	2	29.5
Females	9	..	9	11.41	..	.....
Right	16	2	14	18.25	1	28.0
Left	29	2	27	21.76	1	31.0
Posterior incision	12	3	9	12.11	2	29.50
Anterior incision	29	1	28	14.29	..	.....
Anterior and posterior incisions	..	..	..	.....	..	.....
Type of incision not stated	4	..	..	77.75	..	.....
Movable tumor	11	..	11	20.45	1	31.00
Fixed tumor	5	1	4	5.87	1	28.00
Palpable tumor	22	3	19	17.20	..	.....
Kidney palpable	4	..	4	6.50	..	.....
No palpable tumor	3	..	3	76.60	..	.....
Lesion in lower pole	3	..	3	13.30	..	.....
Lesion in upper pole	1	..	1	.....	..	.....
Lesion involved entire kidney	1	..	1	6.0	..	.....
Lesion median in position	..	..	..	.....	..	.....
Situation of lesion indeterminate	40	4	36	21.72	2	29.50
Tumor large	35	2	33	19.0	1	31.00
Tumor moderate sized	..	..	..	.....	..	.....
Tumor small	..	..	..	.....	..	.....
Size not stated	10	2	8	26.37	1	28.00
Extension into renal vein	4	..	4	4.62	..	.....
No extension into renal vein	41	..	41	14.03	2	29.50
Perirenal tissue involved or capsule broken	26	3	23	13.47	1	31.00
No involvement	19	1	18	29.96	1	28.00
Roentgen ray alone	7	..	7	16.85	1	31.00
Roentgen ray and radium	6	..	6	13.83	..	.....
Radium alone	1	1	..	.....	1	28.00
No radiologic treatment	31	3	28	28.95	..	.....
Carcinoma	10	2	8	15.85	..	.....
Hypernephroma	35	2	33	21.72	2	29.50

for from seventy-two to ninety-six hours, rather than to attempt ligation. Twenty-five of the patients are dead, seven of whom died in the hospital; hemorrhage was an associated factor in three of these seven deaths in the hospital. One patient died from hemorrhage on the day of operation; another, in whom there was a questionable degree of bleeding, died of shock. A third patient died on the fourth postoperative day and death was attributable to secondary hemorrhage. Two patients died of sepsis. One patient died on the fifteenth postoperative day; bronchopneumonia and pleurisy were found at necropsy. Another patient died on the first postoperative day following right nephrectomy. In this instance the

pleura on the right side was accidentally opened and immediately sutured at the time of nephrectomy. At necropsy the right lung was found to be collapsed, and in addition a moderate degree of pleurisy with effusion was present. The average postoperative life in cases in which forceps were allowed to remain on the vascular pedicle was 22.33 months. Five patients have thus far lived an average postoperative life of 85.6 months. This compares favorably with the results in the group of 253 cases in which the vascular pedicle was tied; 167 of the patients are dead, twenty-three of whom died in the hospital and 144, subsequently. The latter patients had an average postoperative life of 28.79 months. Eighty-six per cent of the patients in whom the vascular pedicle was tied had an average postoperative life of 79.97 months.

Nephrectomy and Primary Ureterectomy.—In twelve cases in which nephrectomy was performed, the primary operation involved treatment of the ureter. In ten of these cases, it was necessary to perform nephrectomy and partial ureterectomy. In one case, nephrectomy and ureterectomy were performed; in another, nephrectomy and ureterectomy were done, the ureterectomy including the portion of the ureter that is intramural in the bladder. One of these patients returned later and another operation was done for recurrence. Four of these twelve patients are dead, after having lived, respectively, three, eight, eleven and forty-six months, an average length of life of seventeen months. Seven patients are living; one of these patients has lived seven months, two patients, one year, and the remaining four patients, four years and five months, seven years, nine years and five months, and eight years, respectively. One patient in this group of twelve was not traced.

Nephrectomy and Subsequent Ureterectomy.—Following nephrectomy three patients returned, and subsequent ureterectomy was performed. One patient returned because of gross hematuria associated with typical, severe renal colic, symptoms which developed ten months following nephrectomy. Another patient had profuse, gross hematuria that occurred at practically every micturition; this did not develop, however, until five years after the nephrectomy. Three months following nephrectomy, a third patient suffered from severe lower abdominal pain associated with gross hematuria and the passing of small pieces of tissue at each micturition. One of these patients underwent partial ureterectomy, and the microscopic sections showed the adenocarcinoma to have infiltrated the ureteral wall. This patient lived one year and five months following the second operation. In another patient, ureterectomy was performed; at operation the ureter was found embedded in a mass of recurrent adenocarcinoma; the patient lived one year. The third patient, who required ureterectomy, gave an interesting subsequent history. Microscopic sections of the ureter revealed adenocarcinoma. Shortly after ureterectomy, symptoms developed suggestive of tumor of

the brain. At exploration a specimen was removed from the lesion in the brain and was diagnosed as metastatic carcinoma. The patient lived five years and four months following the nephrectomy.

Judging from this experience, it is doubtful whether removal of the entire ureter at the time of nephrectomy would have offered any better prospects. Probably removal of the upper part of the ureter is indicated and is sufficient in practically all cases of renal carcinoma.

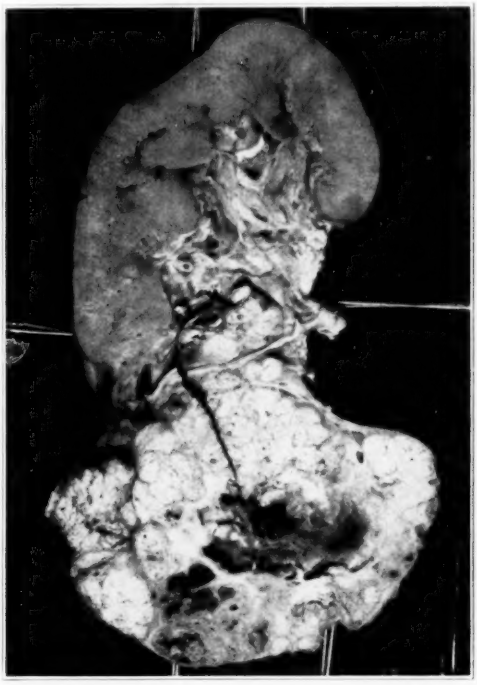

Fig. 8.—Adenocarcinoma involving lower pole of left kidney; subsequent ureterectomy for recurrence five years following the nephrectomy. The patient died three months after ureterectomy. Interim exploration of a tumor of the brain proved it to be metastatic.

RECURRENCE

Definite recurrences were noted in fifty-one cases in which nephrectomy was performed. In six other cases, symptoms and data were present which suggested recurrence. In ten of the fifty-one cases with recurrences the patients returned for surgical procedures. In three cases subsequent ureterectomy was performed (fig. 8), and in one additional

case there was involvement of the lower three ribs on the side from which the tumor was removed. In one case exploration was performed, and a duodenal ulcer was found in addition to the local recurrence. Exploration of the wound was performed in two cases, and in three others tissue was removed from the site of operation. At the primary operation in the cases in which recurrences developed later, the capsule was broken through in three cases and the surrounding tissue was involved in one case. Local recurrences were reported in thirty-one (23.65 per cent) of the 131 cases in which perirenal involvement was noted, or the capsule was reported as broken through by the carcinoma at the time of nephrectomy.

METASTASIS

That carcinoma of the kidney does not remain a local disease, is attested to by the following data: definite metastasis was noted at necropsy in thirty-one instances; in thirteen it was noted at operation; in twenty-three it was found on subsequent examination and in thirty-one instances data recording metastasis were received from the attending physician or from relatives. Visceral metastasis occurred in fifty-six cases. There was involvement of the lungs in thirty, of the liver in thirteen, of the brain in five, of the spinal cord in two, of the spleen in one case, of the portal vein in one, of the heart in one, and of the pleura in three cases. Bony metastasis occurred in eleven cases; the humerus was involved in three, the sternum in one case, the femur in one, the ilium in one, the spinal column in two cases, the acetabulum in one case, the radius in one, and the ribs in one. Lymphatic involvement occurred in seventeen cases; the renal or adjacent nodes were affected in five, the retroperitoneal nodes in five; the aortic nodes in two, the mediastinal nodes in two, the axillary nodes in one case, the supraclavicular nodes in one, and the epitrochlear nodes in one. In fourteen cases surrounding structures were involved by direct extension: the suprarenal gland was involved in two, the ureter in two, the diaphragm in one case, and the peritoneum in three cases; a separate tumor overlay the spinal column in one case; there was intra-abdominal extension in three cases, and extension to the sigmoid in two. Distant metastasis was noted in thirteen of these fourteen cases whereas a definite recurrence occurred in two cases.

Lungs.—Pulmonary metastasis was definite in twenty-four of thirty cases in which there was a subsequent history of pulmonary involvement or in which necropsy was performed. In this group there were eight deaths in the hospital. Necropsy was performed in eight cases; pulmonary metastasis was noted in both lungs in seven cases and in one lung in one case. Preoperative roentgenograms failed to demonstrate any evidence of metastasis in the eight cases in which necropsy revealed that the lungs were involved. In the six cases in which pulmonary

metastasis was present, the patients died within a year; the average length of life was 6.7 months. In the remaining ten cases, the patients lived from 1.5 to 7.5 years; the average length of their postoperative life was six years. In all 186 preoperative roentgenologic examinations of the thorax were made. One hundred and forty-seven (79.03 per cent) were reported as negative. In forty cases (21.50 per cent) there was notation of some condition in the chest other than metastasis.

Bumpus [11] recently reported a case in which there was apparent disappearance of pulmonary metastasis. The patient was a man, aged 59 years, on whom nephrectomy had been performed, Jan. 23, 1924. The tumor had destroyed half of the renal substance. A preoperative roentgenogram of the chest was reported as negative for metastasis. In January, 1925, the patient experienced sharp pain across the chest, associated with bloody sputum. During the next five months, he again noticed bloody sputum on five occasions. He gave an additional history of three attacks of transitory hemiplegia followed by dragging of the left foot. A roentgenogram of the chest, April 6, 1925, disclosed multiple metastatic areas in both lungs. In September, 1925, roentgenograms of the chest were reported as negative for metastasis, and the patient was in splendid health. In April, 1928, more than four years after nephrectomy, roentgenograms of the lungs were negative for metastasis. At the present time, more than five years following nephrectomy, the patient is apparently well.

Nervous System.—In five cases in which nephrectomy was performed, symptoms subsequently developed, suggesting a tumor of the brain. In two of these cases, the patients returned for reexamination. In one of the cases the carcinoma of the kidney was reported as fixed at the time of operation and was diagnosed as adenocarcinoma. Five years later, because of recurrence of hematuria, the remaining ureter was removed and microscopic examination disclosed adenocarcinoma. Four months following this, symptoms developed suggestive of tumor of the brain. Exploration of the brain revealed a lesion that on microscopic examination was reported as hypernephroma. In the other case the growth at the time of nephrectomy had involved the renal vessels. Death occurred after three years. Symptoms developed before death suggesting a definite lesion of the brain stem. The home physician attributed the death of another patient of the five to metastasis to the brain. At the time of nephrectomy four years previously the renal lesion had appeared to be encapsulated and had been diagnosed as alveolar carcinoma. In two of the five cases symptoms developed later which were suggestive of involvement of the spinal cord. In one of these, an

11. Bumpus, H. C., Jr.: The Apparent Disappearance of Pulmonary Metastasis in a Case of Hypernephroma Following Nephrectomy, J. Urol. **20**:185, 1928.

operative note was made that all tumor tissue had not been removed. The patient lived ten months. Symptoms and data suggestive of tumor of the brain were present in two other cases in which operation or necropsy was not performed.

In three additional cases, not included in the five mentioned, observed at the clinic the symptoms were referable to the brain, and a diagnosis of tumor of the brain was made. Necropsy in two of these cases disclosed carcinoma of the kidney with definite metastasis to the brain. In the third case, carcinoma of the kidney was found at necropsy. Although an examination of the brain was not made in this case, the cerebral symptoms were attributed clinically to metastasis. As many of these patients have associated infection and are in the age when arteriosclerosis appears, it is often difficult to state whether or not a certain syndrome is best explained on the basis of inflammation, cerebral arteriosclerosis or metastasis.

ROENTGEN RAY AND RADIUM IN RELATION TO POSTOPERATIVE LENGTH OF LIFE

In addition to nephrectomy, treatment with roentgen rays was instituted in seventy-eight cases. Death occurred in fifty-one of these, after an average postoperative life of 24.37 months. In twenty-seven of the cases in which treatment with roentgen rays was given, the patients are living. The average postoperative length of life thus far has been 46.03 months. Roentgen rays and radium were used in twelve cases; death occurred in all after an average postoperative life of 35.09 months. Radium was used in nine cases, and death occurred in eight of these. One patient died while in the hospital, and seven died subsequently after having lived an average postoperative life of 10.57 months. One patient has been living for ninety-six months.

One hundred and eighty-four patients did not receive treatment with roentgen rays or radium following nephrectomy. Of these 184 patients, 121 are dead; twenty-nine died in the hospital and the remaining ninety-two died subsequently after having lived an average postoperative life of 30.61 months. The patients in sixty-three of the 184 cases in which roentgen rays or radium were not used in addition to nephrectomy are living. The average postoperative length of life, thus far, is 95.12 months.

It will be noted that when roentgen rays or radium were not used, the postoperative life of the patients still living is much longer than was the postoperative length of life in those cases in which treatment by roentgen rays and radium was used. The average postoperative life of patients who are still living and who did not receive treatment by roentgen rays or radium was 95.12 months, as compared with an average postoperative life of 46.03 months for those patients who are living and who received

treatment by roentgen rays alone. The patients who died following nephrectomy and who did not receive treatment by either roentgen rays or radium, postoperatively, lived an average postoperative length of time of 30.61 months, whereas the twelve patients who received treatment by radium and roentgen rays lived an average postoperative length of time of 35.09 months. It must be remembered, however, that the cases in which treatment by roentgen rays and radium was given were for the most part those cases in which all the tumor tissue had not been removed, in which the veins were involved or in which, for some reason, the prognosis was poor. Further, the radiotherapy was not always used

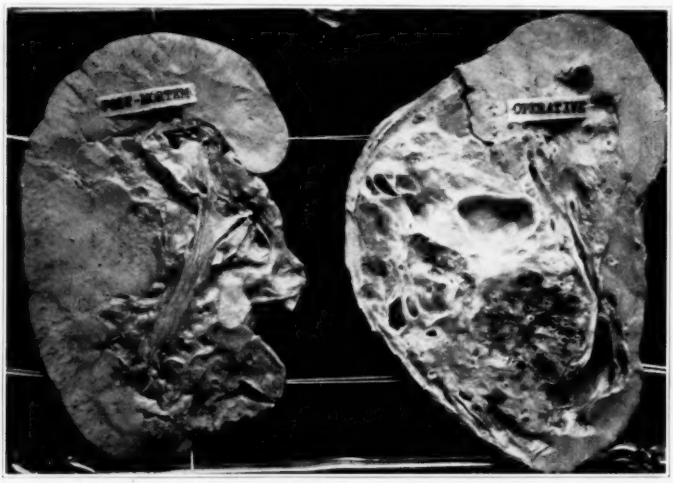

Fig. 9.—Bilateral papillary carcinoma. The patient was a man, aged 65 years, who had had hematuria intermittently for ten months. Five months previous to admission to the clinic he had undergone cystostomy elsewhere and probably a tumor had been removed from the bladder. Death was due to renal insufficiency on the fourth day following nephrectomy.

under supervision of physicians at the clinic, and we are not certain of the manner in which it was used.

BILATERAL HYPERNEPHROMA, HYPERNEPHROMA WITH POLYCYSTIC DISEASE AND HYPERNEPHROMA IN AN ECTOPIC KIDNEY

In one case in which death occurred following nephrectomy for adenocarcinoma, necropsy revealed a hypernephroma, 3.5 by 3 by 1.5 cm., in the remaining kidney (fig. 9). Hypernephroma occurred in one case with bilateral polycystic kidneys. At necropsy the polycystic nature of the remaining kidney was verified. In another case in which poly-

cystic disease was suspected, but in which exploration alone seemed advisable, the patient lived for 4.5 years after operation. A later examination of a specimen removed from a region of metastasis in the arm revealed adenocarcinoma. In one case a huge adenocarcinoma occurred in an ectopic kidney. The mass had been present for six months, and the patient lived one year and nine months postoperatively.

CARCINOMA OF THE KIDNEY ASSOCIATED WITH LITHIASIS

In ten of the cases in which nephrectomy was performed in which the diagnosis was adenocarcinoma, renal lithiasis was associated; in eight the adenocarcinoma was found incidentally. In two cases the diagnosis of neoplasm had been made preoperatively. In four of the eight cases in which the malignant condition was an incidental observation, the patients have lived for eight years each. In one case the patient died in the hospital. In two other cases, there was an associated perinephric abscess, and the patients lived 2.5 years and 1.5 months, respectively. One patient was not traced.

RELATION OF NEPHRECTOMY TO POSTOPERATIVE LENGTH OF LIFE

In 250 of the 283 cases traced in which the patients were subjected to nephrectomy, the diagnosis was adenocarcinoma. One hundred and sixty-seven of these patients are dead; twenty-five died in the hospital, and 142 (63.11 per cent) died after having lived an average postoperative life of 29.67 months. In eighty-three cases (33.86 per cent) in which the patients are now living, the average duration of life has been 84.77 months. In thirty-three of the patients subjected to nephrectomy the diagnosis was alveolar carcinoma; twenty-five of these patients are dead. Five of these deaths occurred in the hospital, and twenty patients (71.42 per cent) died after living an average postoperative life of 16.86 months. In eight cases (28.57 per cent) in which the patients are now living, the average duration of life has been thirty-seven months. It may be noted that a higher percentage of patients in the group with alveolar carcinoma are dead, that is, 71.42 per cent, as compared with 63.11 per cent for the group with adenocarcinoma. The average postoperative length of life in the cases of alveolar carcinoma in which the patients have died was much shorter than the length of life in the corresponding group of patients with adenocarcinoma, 18.86 months as compared with 29.67 months.

The percentage of patients with alveolar carcinoma and with adenocarcinoma who are living is practically the same; however, the average length of life of patients with adenocarcinoma is greater than that of patients with alveolar carcinoma. Patients with adenocarcinoma have lived an average of 80.28 months, whereas those with alveolar carcinoma have lived for an average of thirty-seven months. The longest post-

operative life of any patient with alveolar carcinoma was six years and ten months, whereas twenty-six patients with adenocarcinoma have lived ten years or more.

ANALYSIS OF THE DATA CONCERNING PATIENTS LIVING TEN YEARS OR MORE

In order to determine whether any singular factors might be noted, an analysis was made of the data in cases in which the patients are living ten years or more after operation. In this group of twenty-six patients there were eighteen men and eight women. The average age of the men was 49.77 years and of the women 48.12 years. The right side was involved in fifteen cases, and the left side in eleven. The average duration of symptoms before operation for the group was 36.92 months. The first symptom, in order of frequency, was pain in twelve cases, hematuria in nine and tumor in two; pain and hematuria occurred together in two cases and in one case the symptoms were not stated. A palpable tumor was demonstrated in eleven cases. The capsule was found broken at the time of nephrectomy in two cases, and definite perirenal extension was noted in six. In thirteen cases the gross specimens were recorded as large; in five, as medium, and in seven, as small; the size of one specimen was not stated.

These data show certain interesting comparisons in relation to the general group of patients subjected to nephrectomy. In may be noted that all the specimens were diagnosed as adenocarcinoma; the longest postoperative life in any case in which the diagnosis was alveolar carcinoma was six years and ten months. The average age of the patients was two years less than the average age for the entire group of patients who underwent nephrectomy. In this group in which the patients lived ten years or more, the right side was involved more often than the left side, whereas in the general group there were fewer tumors on the right than on the left side. Forty-two per cent of the patients had palpable tumors, as compared with 77 per cent in the entire group. The percentage of cases in which the renal capsule was broken through or in which perirenal involvement was noted at the time of nephrectomy is 30 for the group of patients who lived ten years, and 36 for the entire group. Of the gross specimens from the patients who lived ten years, thirteen (50 per cent) were recorded as large, whereas 161 gross specimens from the general group (57 per cent) were recorded as large. In six cases (23 per cent) the gross specimens from patients who lived ten years were recorded as medium. Seven (26 per cent) of the gross specimens from patients who lived ten years were recorded as small, whereas thirty-six (13 per cent) of the speicmens from the general group were recorded as small. In the group in which life endured for ten years or more, the percentage of patients presenting

large and moderate-sized tumors is less than for the general group in which nephrectomy was done, whereas the number of patients with small original growths is twice as large for the group in which the patients lived ten years as it is for the general group.

PROGNOSIS

After a careful study of the data which have been set forth, one is impressed with the fact that the prognosis is dependent on many factors. The first factor that should be considered is the degree of cellular differentiation in the carcinoma. In none of the thirty-three cases in which nephrectomy was performed and in which the diagnosis from

Fig. 10.—Papillary adenocarcinoma. The lesion is well encapsulated, and is localized to the upper pole of the kidney. The patient was a man, 46 years of age, who had had intermittent hematuria for eighteen months before operation. The patient is living and well twenty-two and a half years after operation.

microscopic examination was alveolar carcinoma did the patient live more than six years and ten months. On the other hand, in twenty-six of the 250 cases in which the diagnosis was adenocarcinoma (hypernephroma) the patients have lived ten years or more. One of the patients has lived 22.5 years (fig. 10). Symptoms are present for a shorter time, and the postoperative length of life is less among women than among men. Patients with small movable tumors may expect to live longer than those with extensively fixed tumors with involvement of perirenal tissue. The hemoglobin at the time of operation bears a marked relationship to the rate of mortality. A percentage of hemo-

globin of more than 70 offers a good prognosis. Metastasis occurs early and easily escapes detection, as is well demonstrated in seven cases with pulmonary metastasis in which preoperative roentgenograms of the thorax were reported negative, and necropsy shortly after operation showed definite metastasis.

Infection has a bearing on prognosis. It may be associated with obstruction to urinary drainage from blood clots, with obstruction from stones or with mechanical obstruction from extrarenal pressure. Another factor is the toxemia produced by the infection and by the absorption of degenerating tumor tissue.

The immediate mortality rate for nephrectomy was 9.61 per cent; 106 patients (51.45 per cent) have lived three years or more (fig. 11);

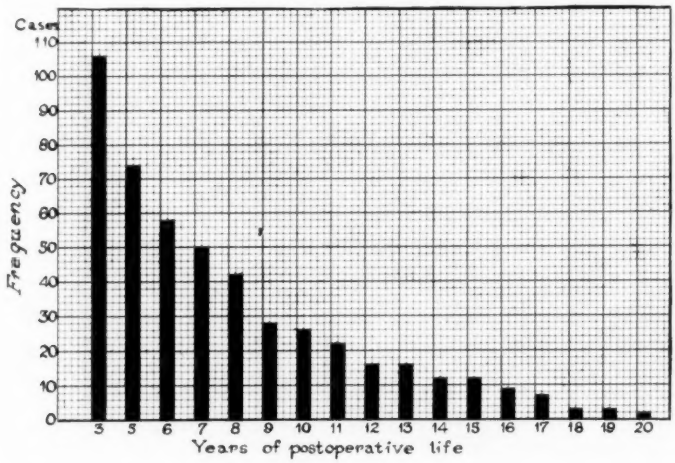

Fig. 11.—Years of postoperative life of 106 patients with carcinoma of the kidney who lived three years or more.

seventy-four patients (35.92 per cent) lived five years or more; twenty-six patients (12.62 per cent) lived ten years or more. One patient, already mentioned in another connection, has lived more than 22.5 years.

SUMMARY

An analysis was made of 367 cases in which operation was advised for carcinoma of the kidney. Of this number, 330 have been traced. We wish to call attention to the fact that this paper includes cases in which operation was performed up to Jan. 1, 1928. Although insufficient time has elapsed since the operations done in recent years to warrant our drawing definite conclusions concerning the postoperative course of the patients, we believe that the general average of preoperative and post-

operative data presents many features worthy of record. Sixty-eight and thirty-nine hundredths per cent of the patients in the entire group were men and 31.60 per cent were women. The average age of the entire group was 51.76 years. The tumor involved the right side in 46.04 per cent of the patients and the left side in 53.40 per cent. Hematuria, pain and tumor were observed as the three cardinal features. Hematuria occurred as the first symptom in 43.86 per cent of the cases, pain in 37.32 per cent and tumor in 13.62 per cent. Of the 283 patients subjected to nephrectomy, who were traced, 192 are dead, having lived an average postoperative life of 23.26 months. There were thirty deaths in the hospital. Ninety-one patients are living, having lived thus far an average postoperative life of 60.88 months. Of forty-seven patients subjected to exploration alone, forty-five are dead, having lived an average postoperative life of 18.78 months. Two are living, one having lived thus far for an average postoperative life of 18.78 months. Metastasis occurred in seventy cases. Recurrence was reported in fifty-one cases. In the cases of involvement of the renal vein, the immediate mortality was not appreciably different from that observed in cases without involvement of the renal vein. However, the number of patients who died postoperatively is much higher among those with involvement of the renal vein.

Surgical approach through a posterior incision and removal of the upper portion of the ureter are significant factors in nephrectomy for carcinoma of the kidney.

The value of roentgen rays, radium or both as additional aids to surgery is difficult to estimate, since they are used only in those cases in which the prognosis is poor, namely, in cases in which there was extensive involvement of perirenal tissue and in which it was felt that all the tumor tissue was not removed. Treatment by roentgen ray in some of these cases was not always used under supervision of physicians of the clinic.

CONCLUSION

Carcinomas of the renal cortex are extremely malignant and are often well advanced before producing symptoms. Alveolar carcinomas, or those showing less cellular differentiation, are the most highly malignant, whereas adenocarcinomas (or papillary adenocarcinomas) are less malignant, as judged from their clinical course. Better end-results are dependent on earlier medical consultation by the patient after the onset of the initial symptom or sign. The end-results, as exemplified in the 106 cases in which the patients lived from three to 22.5 years, we believe justify nephrectomy for renal carcinoma.

EOSINOPHILIC HYPERLEUKOCYTOSIS IN HODGKIN'S DISEASE WITH FAMILIAL EOSINOPHILIC DIATHESIS

REPORT OF A CASE AND REVIEW OF THE LITERATURE*

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Moderate leukocytosis and slight eosinophilia have long been regarded as common components of the clinical picture of Hodgkin's disease. In few cases of authentic Hodgkin's disease, however, has there been recorded an excessive increase in eosinophilic cells of such magnitude as to warrant the designation "eosinophilic hyperleukocytosis." Such hyperleukocytosis, with absolute eosinophilia, has also been mentioned in association with various other unrelated diseases and has been described independently as an unclassified clinical syndrome. The following case is reported because, as a case of Hodgkin's disease, it is unique, both in the height of the leukocyte count and in the percentage and absolute number of mature eosinophils; and also, because it offers a possible explanation for this most unusual response of the bone-marrow.

REPORT OF CASE

History.—E. H., a woman, aged 35, was admitted on Sept. 14, 1928, to the University Hospital, service of Dr. Alfred Stengel, with enlarged nodes in the neck, cachexia, and irregular fever. Her illness dated back to 1918, when, following an upper respiratory infection, a transient swelling of the glands of the right side of the neck was first noticed. This swelling apparently disappeared and recurred at intervals. In 1921, another group of glands at the base of the neck became enlarged. Free use of iodine for several months was without effect. There was no fever and only slight loss of vitality. The weight, at that time, was 125 pounds (56.7 Kg.). The condition remained unchanged, except for some variation in the size of these nodes, until August, 1925, when quite suddenly there appeared a marked swelling of all the cervical glands on the right side. This condition persisted unchanged. In May, 1926, a tonsillectomy was performed. Microscopic study of the tonsils showed only "chronic inflammation." In the spring of 1927, two nodules appeared in the left popliteal space and shortly thereafter tender masses in both inguinal regions. Treatment with ultraviolet rays was ineffectual. During the fall of 1927, the patient was given tremendous doses of mercury and arsenic, by mouth. The reasons for this particular medication could not be elicited. Following this, the patient suffered a severe dermatitis (arsenical?), lasting several weeks. Coincidentally, the glandular enlargements entirely disappeared, only to recur to their previous size within a few weeks.

* Submitted for publication, July 9, 1929.

* From the Medical Division, Hospital of the University of Pennsylvania.

Weakness and loss of weight then became evident. A biopsy on a cervical gland in February, 1928, was reported to have shown only a chronic inflammatory process. Subsequently, all the symptoms of anemia, afternoon fever, severe sweats, diarrhea, and loss of strength and weight developed in rapid succession. The glands increased slightly in size, the lumps were noted in the right breast and in the abdomen. The past history and family history will be considered later.

Physical Examination.—Significant data only are presented. The temperature was 102 F.; the pulse rate, 100; respirations, 22; blood pressure, 108 systolic and 48 diastolic. The weight was 85 pounds (38.6 Kg.). The patient was extremely

Fig. 1.—Patient E. H. The massive enlargement of the cervical lymph nodes of the right side of the neck should be noted.

emaciated, with a sallow, shiny, yellowish-tinted skin, and was obviously anemic and asthenic. The most striking feature was the glandular enlargement, as illustrated in figure 1.

The glands were quite firm, painless, discrete and freely movable beneath the skin. All of the cervical glands were enlarged, especially those on the right side of the neck. A few glands were found in both axillae, in the inguinal and femoral regions, in both breasts, and retroperitoneally. On the right side, the inguinal and femoral glands were extremely tender and soft.

The conjunctivae and mucous membranes were pale. Ophthalmoscopic examination revealed punctate retinal hemorrhages in both fundi. The heart was not enlarged. A loud blowing systolic murmur was audible everywhere over the precordium. The pulses were slapping, soft and easily compressible. The edge of the liver, which was palpable 3 cm. below the right costal margin, was firm, rounded and smooth. The tip of the spleen was easily palpable 2 cm. below the left costal margin.

Course.—During the three months in the ward, the patient became steadily and progressively weaker. An irregular temperature varied from a subnormal level up to 103 F., and only subsided as a terminal event. Chills and severe sweats were not infrequent. Repeated transfusions maintained the red blood

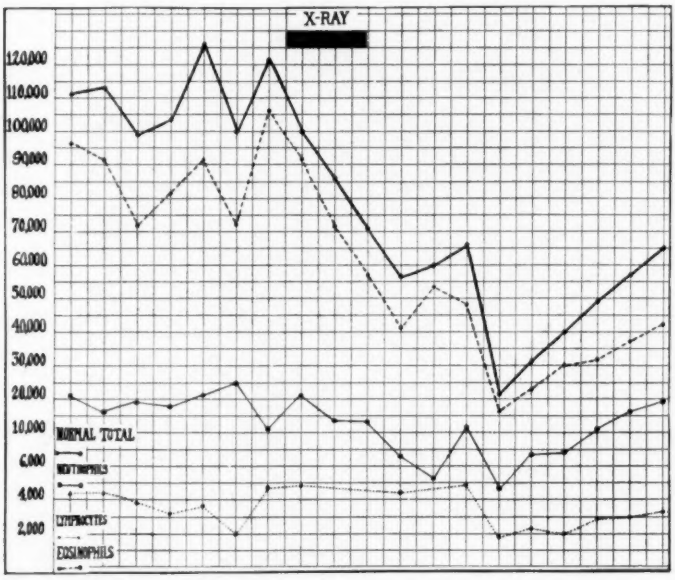

Fig. 2.—Graphic representation of the differential leukocyte counts in absolute numbers, taken at four day intervals, showing the effect of roentgen treatments.

corpuscles at a safe level without improvement. A course of roentgen treatments was given over the long bones, abdomen and neck glands, and was finally discontinued because of vomiting and weakness. The effectiveness in reducing the size of the glands and the total leukocyte count were striking, as shown in figure 2. The retroperitoneal glands disappeared, the cervical glands became smaller, and the liver and spleen were perceptibly reduced in size. In spite of these encouraging results, the retrograde course continued; the liver suddenly became tremendously swollen, the heart action became weaker, and moist râles appeared at the bases of both lungs. Following several convulsions, the patient became comatose, the lungs filled with râles, and death ensued on Dec. 27, 1928, as a result of cardiac collapse. The apparent duration of the disease, as estimated from the history of glandular swelling, was seven years.

Laboratory Data.—The urine showed only a trace of albumin, a few white cells and hyaline casts. The Wassermann reaction of the blood was repeatedly negative. Blood chemistry studies were all within normal limits. Roentgen examination of the chest revealed no definite mediastinal involvement. There was a low free acidity of the gastric contents. The basal metabolic rate was + 3 per cent. Skin sensitivity tests for the various foods, pollens and animal dander allergens and for arsenic were all negative. Because of the condition found on study of the blood, careful and repeated examinations of the stools were made, but no parasites or ova were seen.

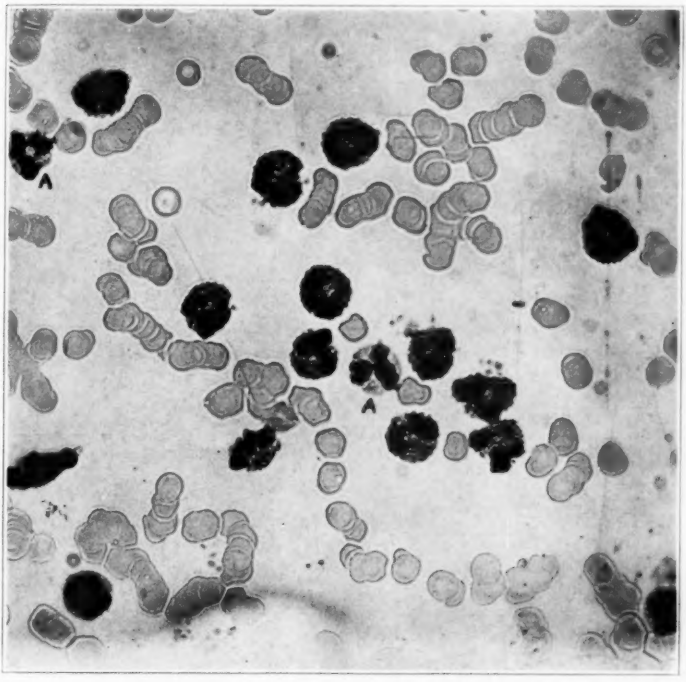

Fig. 3.—Blood film (Wright stain). Typical field, showing mature polymorphonuclear eosinophils and two polymorphonuclear neutrophils (*A*).

Cytologic Study of the Blood.—The studies were made by Dr. Thomas Fitz-Hugh, Jr., of the department of hematology of the Hospital of the University of Pennsylvania. The observations of greatest interest in this case were the hyperleukocytosis and the persistent, high eosinophilia. Figure 2 shows an average total leukocyte count of more than 100,000 before roentgen treatments were instituted, and an analysis of the differential count reveals a percentage of eosinophils varying from 72 to 90. The polymorphonuclear neutrophils averaged 18 per cent and the lymphocytes, 4 per cent.

After the roentgen treatments, there was a progressive decrease in leukocytes to 20,000, with a gradual rise again after it was discontinued. In spite of this

precipitous fall in the leukocyte count, the differential count remained unchanged. By a comparison of the total number of each type of cell, it is apparent that the eosinophils account for the hyperleukocytosis, whereas the neutrophils, lymphocytes and large mononuclears are only slightly increased in total number above the proportion found in the majority of cases of Hodgkin's disease.

Practically all of the eosinophils were typical mature cells, with two or more lobulations of their nuclei, and large, highly refractile red granules of equal size

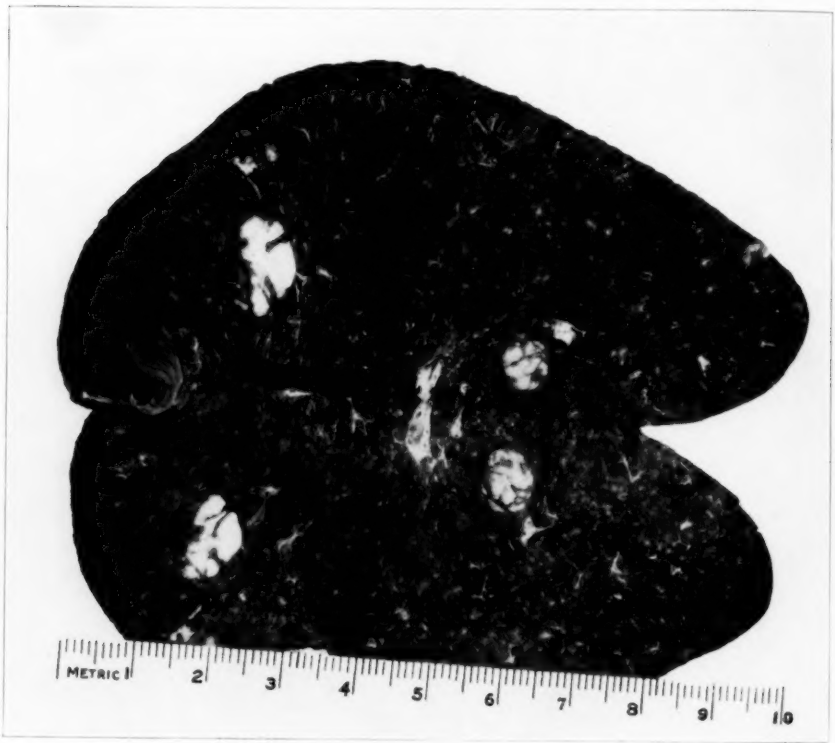

Fig. 4.—Cross-section of spleen, showing nodular masses and diffuse fibrosis.

filling the cytoplasm. A few of the neutrophils were of the young type, classified as metamyelocytes, but no true myelocytes were seen in any of the examinations of the blood.

The red blood cell count was characteristic of a rather severe secondary anemia, averaging 2,800,000 cells, with a hemoglobin content of 45 per cent (Sahli). There was moderate anisocytosis and poikilocytosis. The platelet count remained around 130,000. In spite of frequent transfusions, there was only a slight improvement of the blood picture. The hemoglobin rose from 34 to 55 per cent, and the red blood cells from 2,400,000 to 3,000,000, with a decrease in anisocytosis.

Autopsy.—Significant data only are given. Autopsy was performed by Dr. George Robson, of the department of pathology of the University of Pennsylvania.

Gross Examination: The spleen weighed 250 Gm. and measured 11 by 10 by 5.5 cm. The surface was firm and smooth, and mottled with dark red blotches. Cut sections showed diffuse fibrosis. Scattered through the organ were a number of grayish-white tumor masses, composed of soft, friable tissue definitely circumscribed and from 1 to 12 mm. in diameter.

The liver weighed 1,630 Gm. and measured 23 by 19 by 8.5 cm. The consistency was normal. The cut surface showed nutmeg mottling with pale yellow zones in the periphery of each lobule. The suprarenals weighed 3.9 and 5.6 Gm. Both were smaller than normal and showed marked lipoid exhaustion.

The architecture of the kidneys was grossly normal. Engorged medullary rays formed a striking contrast with the pale, mottled cortex. The abdominal lymph nodes were composed of chains of enlarged nodes along the iliac vessels extending up along the aorta and vertebrae where the nodes were larger and partially fused. The lower portion of the aorta and the upper portions of the iliac vessels were embedded in rather firm tissue which, on cut surface, showed enlarged lymph nodes of somewhat indistinct outline, and surrounded by white bands of fibrous tissue. Along the bodies of the lumbar vertebrae, especially on the right side and extending up to the diaphragm, there was a large grayish mass made up of fused lymph nodes. After removal of parts of the lumbar vertebrae, there was seen an actual invasion of this tissue through the periosteum into the bodies of the vertebrae to a depth of from 4 to 6 mm. The lumbar muscles, which were in contact with the paravertebral mass, were also involved. The lymph nodes about the celiac axis and in the mesentery and omentum were all slightly enlarged and quite firm. The superficial glands have been described.

The femoral bone-marrow was a uniformly dull grayish red.

Microscopic Sections: Numerous sections of lymph glands taken from various parts of the body showed different stages and degrees of the same process. In a slightly enlarged pinkish-gray mesenteric node the lymph cords were intact, but the sinuses were dilated and lined by swollen endothelial cells. The sinuses contained many actively phagocytic large mononuclear cells, apparently derived from their endothelial lining by desquamation, together with rather numerous red cells and eosinophils. The lymph cords were intact but showed a few large pale endothelioid cells, closely packed lymphocytes, a few plasma cells, and numerous eosinophils. Occasional giant cells of the Reed type were seen. This picture of the highly cellular stage of Hodgkin's disease, with complete loss of typical architecture, was presented by most of the glands. Some, however, showed more advanced stages with dense fibrosis and small scattered cellular areas, composed of endothelioid cells and lymphocytes, but with relatively few eosinophils. All intermediate states between the highly cellular and the densely fibrotic types were represented.

Sections from the large grayish tumor-like paravertebral mass showed a uniformly cellular structure devoid of any of the architecture of a normal lymph node but resembling the cellular type of node already described. These sections were especially rich in eosinophils and showed giant cells of the Reed type. The adjoining muscle was diffusely invaded.

A section from one of the lumbar vertebrae which was in contact with the paravertebral mass also showed invasion. The bone was completely destroyed, except for a few spicules, and was replaced by a cellular tissue of identical structure.

The capsule and trabeculae of the spleen were relatively normal. The red pulp was strikingly engorged with blood and the dilated sinusoids lined by swollen endothelial cells. Numerous eosinophils were seen in the sinusoids. The follicles were inconspicuous. The general pulp showed no evidence of Hodgkin's disease. The nodular lesions, noted in the gross description, proved to be fairly definitely circumscribed but nonencapsulated cellular lesions of a structure identical with that of a paravertebral mass. Small necrotic and hemorrhagic areas were also present.

Many of the central arterioles were remarkable in appearance, because of a proliferative endo-arteritis frequently associated with thrombosis. This had pro-

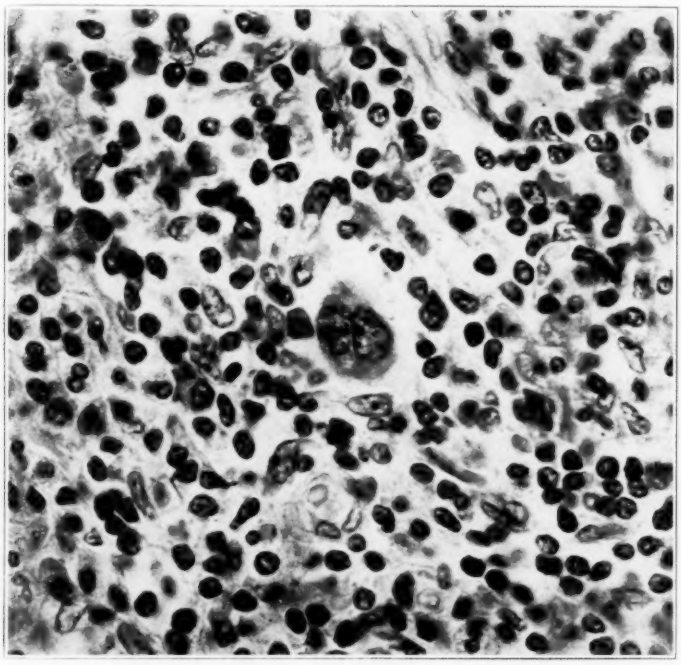

Fig. 5.—Lymph node (eosin-hematoxylin stain). A typical Dorothy Reed cell in the center of a field closely packed with lymphocytes, numerous large pale endothelioid cells, and eosinophils.

duced partial or complete occlusions in the affected vessels. This change was also present in the small arteries of the lymph nodes, kidney and liver, but was most pronounced in the spleen.

The architecture of the liver was normal. Passive congestion, parenchymatous degeneration, fatty infiltration and, in certain periportal areas, Hodgkin's tissue were seen.

There was cloudy swelling and passive congestion of the kidneys. In the outer zone of the cortex, in the interstitial tissue, were found small, dense collections of cells, similar to those found in the lymph nodes.

There was little adipose tissue in the bone-marrow. It was composed almost entirely of active hemopoietic tissue with a predominance of the cells of the granulocytic series. There were many eosinophilic myelocytes and phagocytes filled with deposits of hemosiderin. There was nothing to suggest Hodgkin's granuloma in the sections of bone-marrow.

A note by Dr. Herbert Fox, Director of the William Pepper Laboratory, Hospital of the University of Pennsylvania, stated: "A review of the sections reveals that the lesions are certainly consistent with the diagnosis of lymphogranuloma of the Hodgkin's type. There is one lymph node devoid of Hodgkin's histology,

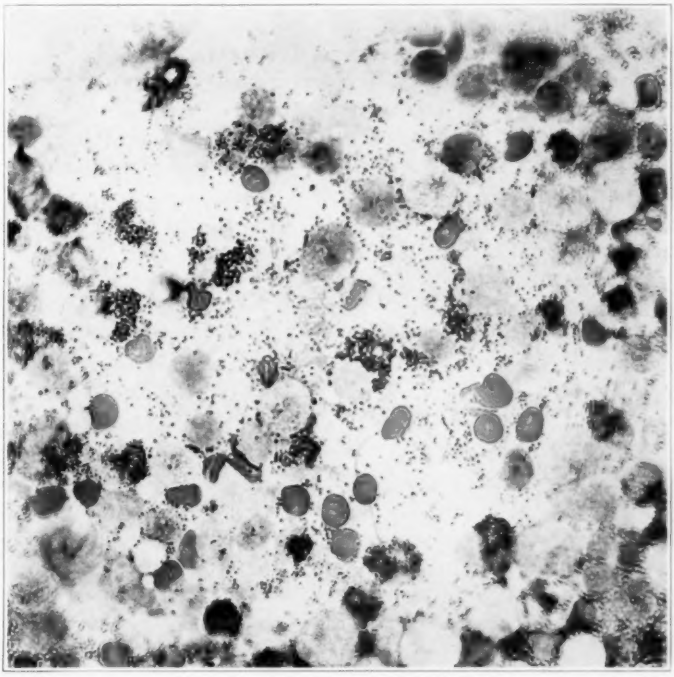

Fig. 6.—Smear of bone-marrow (Wright stain) illustrating engorgement with eosinophilic myelocytes. The scattered eosinophilic granules should be noted.

but it shows a very definite reticulo-endothelial hyperplasia, possibly a part of this process, possibly due to some other unexplained cause. There is a noteworthy change in the small blood vessels in all tissues. It is a tendency to productive meso- and endo-arteritis, with a tendency to thrombus formation.

"The most striking cellular character of all this tissue is eosinophilia. Where the lymphogranulomatous tissue is most cellular and least fibrous, and probably that part where it is the youngest, the eosinophilia is the richest. The bone marrow is hyperplastic in the myeloid series and eosinophils are the most numerous single cells."

COMMENT

Clinically and histologically, this case was one of Hodgkin's disease, but it differed from Hodgkin's disease in its remarkable eosinophilic hyperleukocytosis. Only a few cases showing similar hematologic manifestations have been reported, but no authentic case of Hodgkin's disease showing such a marked eosinophilic diathesis was discovered in the literature. The problem of great interest is the interpretation of the blood picture in this case.

For a quarter of a century, since Goldman [1] first observed eosinophils in the lymph glands in a case of Hodgkin's disease, eosinophilia has been recognized as an integral part of the histologic picture in this condition. The presence of eosinophils was emphasized by Sternberg,[2] Reed,[3] Longcope [4] and others, although the diagnosis of Hodgkin's disease may be made with equal certainty in their absence. It seems, therefore, that eosinophilia in the majority of cases is a specific reaction of the bone-marrow in Hodgkin's disease.

Excessive eosinophilia, somewhat comparable to the author's case, has been recorded as occurring in supposedly true cases of Hodgkin's disease in few instances. The most marked cases that have been found reported in the medical literature are those listed in tables 1 and 2. Only two of these approximate the case reported here in the magnitude of the eosinophilia.

It is not impossible, in view of the similarity to the author's case, that some of these cases may belong to the Hodgkin's group. The diagnosis of eosinophilic leukemia has been suggested, but not accepted, as a clinical or pathologic entity. Admitting, for the sake of discussion, that eosinophilic leukemia exists, one could make out a case for this diagnosis in this patient (see Dr. Fox's note). Against this view, however, are the following observations: (1) the typical Dorothy Reed cells which were found in most of the biopsy and autopsy material examined in the patient; (2) the absence of myelocytic eosinophils in the blood stream, and (3) the fact that one of the large tumors of the lymph nodes failed to show the marked infiltration with eosinophils that characterized the other tumors, and

1. Goldman, E. E.: Beitrag zu der Lehre von dem malignen Lymphom, Centralbl. f. allg. Path. u. path. Anat. **3**:665, 1892.

2. Sternberg, C.: Ueber eine eigenartige unter dem Bilde der pseudoleukämie verlaufende Tuberculose des lymphatischen Apparates, Ztschr. f. Heilk. **19**:21, 1898.

3. Reed, D. M.: On the Pathological Changes in Hodgkin's Disease, with Especial Reference to Its Relation to Tuberculosis, Johns Hopkins Hosp. Rep. **10**:133, 1902.

4. Longcope, W. T.: On the Pathological Histology of Hodgkin's Disease, with Report of a Series of Cases, Bull. Ayer Clin. Lab. **1**:4, 1903.

that one would postulate as necessary if this case were truly one of eosinophilic leukemia. It is assumed, therefore, that this case is acceptable as a proved case of Hodgkin's disease. The chief problem is to account for the remarkable eosinophilic diathesis.

TABLE 1.—*Cases from the Literature*

Name	White Blood Cells	Percentage of Eosinophilia	Absolute Number of Eosinophils
Bunting: Bull. Johns Hospkins Hosp. **25**: 173, 1914	20,000	68	13,600
Bunting	20,000	36	10,800
Barron: Tr. Sect. Pract. Med., 1923, p. 309...	55,000	44	24,200
Bonanno: Policlinico **33**: 1008, 1926.....	29,000	68	19,720
Dimmel: Wien. Arch. f. Inn. Med. **13**: 283, 1926	16,000	26	4,160
Lincoln: Boston M. & S. J. **158**: 677, 1908..	49,000	68	33,320
Pepper: Bull. Ayer Clin. Lab. **4**: 22, 1907....	28,000	16	4,480
Weber and Bode: Lancet **2**: 806, 1927.....	11,000	50	5,500

TABLE 2.—*Further Literary Review**

Author	Diagnosis	White Blood Cells	Percentage of Eosinophils	Absolute Number of Eosinophils	Percentage of Myelocytes
Glanzmann: Deutsches Arch f. klin. Med. **118**: 52, 1915	Lymphogranulomatosa	183,000	33	60,390	2.6
Giffin: Am. J. M. Sc. **158**: 619, 1919	Eosinophilia with splenomegaly	211,000	90	189,900	0.2-0.7
Shapiro: Tr. New York Path. Soc. **19**: 73, 1919	Eosinophilic leukemia	236,000	79	186,400	0.6-5
McDonald and Shaw: Brit. M. J. **2**: 966, 1922	Eosinophilia with splenomegaly	138,000	80	110,400	0.7-4.7
Bass: Am. J. M. Sc. **170**: 416, 1925	Eosinophilia with splenomegaly	25,000	64	16,000	6
Stillman: M. Rec. **81**: 594, 1912	Myelogenous leukemia with eosinophilia	165,000	69	113,850	1.8
Alexander: J. Lab. & Clin. Med. **9**: 803, 1924	Atypical myeloid leukemia	150,000	34	51,000	0.2
Schmidt-Weyland: Med. Klin. **21**: 1707, 1925	Eosinophilic leukemia	90,000	67	60,300	.....
Sibley: Brit. J. Dermat. **27**: 52, 1915	Lymphadenoma	28,150	39	10,978	.....
Rheinbach: Arch. f. klin. Chir. **46**: 486, 1893	Lymphosarcoma	120,000	48	57,600	.....
Aubertin and Giroux: Presse méd. **29**: 314, 1921	Ayerza's syndrome	26,000	70	18,200	.....
Dunger: München. med. Wchnschr.	Carcinoma of colon	35,330	60	21,198	.....
Hay and Evans: Quart. J. Med. **1**: 167 (Jan.) 1929	(1) Acute eosinophilic leukemia	72,187	83	59,915	3.8-5
	(2) Eosinophilic erythroleukemia	46,375	50	23,187	.....

* This table presents another small group of cases of lymphogranulomatous type with comparable hemocytologic manifestations. In this table are also included several unrelated cases with the same type of blood picture.

Weber and Bode advanced the theory that lymphogranulomatous involvement of the intestinal tract might have caused "a protective allergic reaction against absorbed foreign protein, or abnormal products of albuminous catabolic metabolism within the body." The

case of Schmidt-Weyland offered a similar explanation. Many cases, however, have been reported which showed extensive gastro-intestinal involvement by tumor without eosinophilia. McDonald and Shaw and Aubertin and Giroux suggested chronic anoxemia as a factor in the production of eosinophilia. Giffin stressed the chemotactic theory on the basis of toxemia with chronic infection. Lincoln, in his report of a case of Hodgkin's disease, hinted that the dyspnea in his patient might possibly have been true asthma and that the excessive eosinophilia could have been explained on an allergic basis.

In cases like the one here reported and those referred to, in which the tremendous eosinophilic hyperleukocytosis is so far out of proportion to the usual picture of primary pathologic change, it seems not unreasonable to believe that other factors may have been introduced. Therefore, all the usual causes of eosinophilia were investigated in relation to this patient, Mrs. E. H. Some interesting information was thus brought to light.

From the age of 2 to 7 years, the patient had frequent attacks of severe bronchial asthma. At the age of 7 the seizures stopped spontaneously and did not recur. In spite of the fact that a large number of skin tests showed no reaction, an allergic phenomenon must be considered as one of the probable factors in the explanation of the eosinophilia. This lead naturally suggested the importance of investigating the patient's relatives and her family history from the standpoint of allergy. The patient's paternal grandmother had severe asthmatic attacks for many years. Her mother had chronic eczema of the scalp. She presented herself for examination of the blood and was found to have from 5 to 6 per cent of eosinophils on three separate occasions. Two of the mother's brothers have had chronic eczema for years. No blood studies were obtained. The patient's brother has eczema and 6 per cent eosinophilia. Finally, the patient's son, who has had urticaria, showed from 7 to 8 per cent eosinophilia on three separate occasions.

This is an unusual example of allergic manifestation in four generations of a family, with abnormal blood eosinophilia in three generations. Only five case reports of so-called familial eosinophilia were found in the literature. In 1911, Klinkert [5] recorded the case of a family of six, the father and five children, with eosinophil counts of from 7 to 15 per cent, and with hypersensitivity to foods, urticaria, angioneurotic edema and asthma. Fanton [6] recently reported eosinophilia

5. Klinkert, D.: Das Problem der konstitutionellen Eosinophilie, Ztschr. f. klin. Med. **89**:156, 1920.

6. Fanton, E.: So-Called Eosinophil Diathesis, Clin. pediat. **10**:295 (May) 1928.

in a father and daughter with no allergic history. Gaugain [7] observed a family in which the mother had 19 per cent eosinophils and three children, 10, 14 and 15 per cent, respectively, without any demonstrable cause. Cirio's [8] report was that of a healthy man with 66 per cent eosinophils, whose brother and children showed an eosinophilia of from 6 to 15 per cent. Lastly, the case of Bastai [9] was that of a girl, aged 17, whose mother and sister had an eosinophilia of 33 and 32 per cent, respectively, and who herself, had 27 per cent. During the course of an acute infection, the eosinophilia rose to 51 per cent.

An additional cause of eosinophilia in this patient may have been the dermatitis which followed massive arsenical therapy, even though the dermatitis had disappeared long before the patient came under observation. It is well known that dermatoses, in general, and arsenic poisoning, in particular, frequently produce eosinophilia.[10]

SUMMARY AND CONCLUSIONS

A case of Hodgkin's disease is presented, with report of the autopsy, which showed a tremendous eosinophilic hyperleukocytosis together with a marked increase of eosinophils in the bone marrow and the affected lymph nodes. The literature is reviewed. The exaggerated eosinophil response in this case is apparently due to (*a*) a well established familial allergic background, (*b*) a familial eosinophilic diathesis, (*c*) a personal allergic background, (*d*) the specific eosinophil stimulating effect of Hodgkin's disease itself and (*e*) the added effects of arsenic therapy.

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7. Bezançon and Moreau: L'éosinophilie dans le diathèses et les états anaphylitique; Reference to Gaugain's Family, Ann. de méd. **2**:85, 1914.

8. Cirio, L.: Sopra un caso di cosidetta eosinofilia constituzionale, Riforma med. **42**:219, 1926.

9. Bastai, P.: Della eosinofilia constituzionale, Haematologica, 1923, part 1.

10. Latham, J. R.: Exfoliative Dermatitis Due to Arsphenamine, J. A. M. A. **73**:15 (July 5) 1919. Moore, J. E., and Foley, F. E. B.: Serious Reactions from Salvarsan and Diarsenol Brands of Arsphenamin; Unusual Blood Pictures, with Report of a Fatal Case, Arch. Dermat. & Syph. **1**: 25 (Jan.) 1920.

Book Reviews

DIE BEDEUTUNG DES RETIKULOENDOTHELIALSYSTEMS FÜR DAS STREPTOKOKKENSEPSISPROBLEM. By PROF. DR. N. LOUROS and DR. H. E. SCHEYER (der Staatlichen Frauenklinik Dresden) unter Mitwirkung von Dr. A. Schmechel and DR. E. GAESSLER. Price, 14 marks. Pp. 96, with 13 illustrations and 4 colored plates. Leipzig: Georg Thieme, 1928.

Stimulated by their interest in puerperal fever and septic abortion the authors undertook a systematic investigation of the general problems of septicemia caused by *Streptococceae*. This monograph summarizes the results of their experimental work on white mice in which several strains of streptococci of various degrees of virulence were employed. Attention was directed particularly to the reticulo-endothelial system in an effort to gain a better understanding of its rôle in combating such infections.

Certain morphologic and tinctorial changes in the cells of the reticulo-endothelial system are described, which the authors consider indicative of their functional capacity as a defense mechanism. In a search for agents which can stimulate the reticulo-endothelial system to heightened activity an enormous number of experiments were performed in which the microscopic observations were correlated with the ultimate outcome of the infection.

It was found that "blockade" with trypan blue and colloidal iron rendered mice more susceptible to infection. The parenteral administration of aqueous solutions of certain carbohydrates and of mineral salts and the feeding of vitamins was ineffective. On the other hand, various proteins and protein degradation products markedly increased the animal's resistance. Manganese chloride alone, of the heavy metal salts, had a similar though less striking effect. So did certain of a large series of lipoids and acid and alkaline buffer solutions, though still less marked. Roentgen irradiation in proper doses also rendered mice somewhat less susceptible. Various combinations of these methods of treatment were tried with the hope that a summation of beneficial effects might result, but they were all unsuccessful.

Immunization with killed and living cultures in proper doses rendered mice resistant to lethal doses of organisms. No immunity followed the injection of small numbers of streptococci into subcutaneous ajar foci. In many instances mice could be immunized against infection with toxin-producing strains by previous treatment with filtrates of old cultures, but the immunity was strictly strain specific. Vaccination with nontoxin-producing strains failed to raise the resistance to inoculation with toxin-producing strains. Antitoxic and antibacterial horse serums prepared by various commercial firms failed to protect, and in fact, one such serum seemed to increase the susceptibility of recipient animals to infection with the homologous strain.

The authors have performed an enormous number of experiments in a systematic fashion and they might have presented their results in a somewhat more convincing form. The number of protocols, for instance, is negligible. It is surprising that no cognizance is taken of the recent work of certain American investigators, particularly that of Swift and his co-workers, which is pertinent to some of their immunologic observations.

OLD AGE. By ALDRED SCOTT WARTHIN, Professor of Pathology at the University of Michigan. Price, $3. New York: Paul B. Hoeber, Inc., 1929.

The author describes the curve of life as made up of three periods: an ascending portion corresponding to the period of growth; a plateau of from 15 to 20 years representing maturity, and finally, a descending curve corresponding to retrogression and terminating in senescence. The biologic purpose of life is reproduction, "a potential immortality of its kind." Senescence begins at 60 with evidence of body

changes, but frequently without deterioration of the mental faculties. The only escape from senility is death from disease. Rejuvenescence is impossible. The increase in the span of life only increases the number of persons who reach this undesirable state. With this gloomy aspect, the reader looks forward with anticipation to the last chapter which deals with old age, the miseries and the methods of making the most of an undesirable condition. To those who reach this period with retained mental faculties added to the ripe experience of years, there may be much happiness, especially if the victim has been able to acquire hobbies which keep the mind young. In the author's description of senility, nothing gruesome has been omitted.

In this book, the author has given one the unvarnished truth. The person approaching three score, who reads this last chapter before retiring, is not apt to have pleasant dreams. After all, the author is a pathologist and not a practicing physician. His impressions of old age are obtained largely from the morgue. The physician, however, who is familiar with the family life, realizes that old age is not so gruesome. A picture of this period, with loving children, friends and grandchildren, is attractive and often inspiring.

LA FISIOPATOLOGIA CLINICA E SPERIMENTALE DELLA LIPEMIA. By MICHELE BUFANO. Paper. Pp. 300. Milan: Soc. An. Istituto Editoriale Scientifico.

This is an excellent review of a difficult subject. The work is paper bound and of 300 pages without illustrations. It is the best monograph on the fats in many years, and should be made available to American readers.

The fatty acids, cholesterol, lecithin and all the lipoids are included in the studies, and the material is excellently coordinated so that the best possible insight is given into the little known field of the lipoids. The first few chapters cover the chemistry of these bodies in detail, and the various quantitative methods recently devised for their estimation. There follow chapters on the changes in the blood fat and various lipoids under physiologic conditions, such as starvation, exercise, feeding, etc. A serious attempt is then made to draw deductions from these data as to the metabolism of these substances and their physiologic significance. While exception might be taken to many points here brought up, it is probably the best that can be done in the present confused state of the problem.

The rest of the monograph is divided into a series of chapters on the fats and lipoids in various pathologic conditions in which they are known to be disturbed. The search through the world's literature has been thorough, and there is often added significant experimental work by the author. The diseases thus studied and reviewed include among many, diabetes, blood dyscrasias, nephropathies, neoplasms and infections.

WILLIAM HARVEY. By ARCHIBALD MALLOCK. Price, $1.50. Pp. 103, with 18 illustrations. New York: Paul B. Hoeber, Inc., 1929.

This small volume of 100 pages is presented as a sketch of the life of William Harvey. In an age when the demand for condensation and selection is insistent and full biographies are not apt to be generally read, particularly by medical students and practitioners, a volume of this character meets an actual need. While Harvey and his work are, of course, inseparable, the author deals not so much with the evolution of his scientific achievements as with the sort of man Harvey was. His early training, contemporary influences and historical setting are delightfully depicted. One sees the master going about his daily work absorbed in his thoughts on the physiology of the circulation and exhibiting certain amusing idiosyncrasies in behavior, but by no means insensitive to the movement of life about him. One gathers the impression that while he was conscious of the importance of his own contribution to medicine, he was possessed of the dignified modesty characterizing all the truly great spirits of the past.

The book is well illustrated and contains an extensive bibliography. It constitutes a valuable addition to the series of pocket biographies put out by the same publishers.

L'URÉMIE CONVULSIVE. Par le DOCTEUR HENRI THIERS, Interne des Hôpitaux, Lyon. Paper. Pp. 226. Imprimerie Bosc Frères et Riou, 1928.

This book can be recommended to those who desire to read in good French a review of past and present opinions of French observers of uremia in general and the occurrence of uremic convulsions in particular. Little mention is made of contributions not written in French. Twelve cases observed by the author are related. In his conclusions he states that convulsions may occur in any renal condition capable of producing uremia, but comments on their rarity in tuberculous and "surgical" diseases of the kidney. Convulsions often occur after diminution of edema and are more frequent in persons with history of previous nervous ailments or of syphilis. Stress is laid on the diagnostic importance of lumbar puncture as meningeal and cerebral diseases often are associated with or may simulate uremia. Thiers states that the cause of convulsive uremia remains entirely unknown but attaches some importance to Blum's ideas of "uremic cerebral dysmineralization." He is puzzled, however, by the constancy of chloride retention in all kinds of uremia and by the rarity of convulsions.

GALLENSEKRETION UND GALLENENTLEERUNG. By DR. D. ADLERSBERG. Price, 5 marks. Pp. 76, with 4 illustrations and 12 tables. Leipzig: Franz Deuticke, 1929.

The author publishes in monographic form his clinical and experimental observations on the secretion and flow of bile, citing the literature as it bears on the subject under discussion. He finds that pituitary in man has, at the same time, a cholekinetic and an anticholeretic action, and has considerable diagnostic significance in disease of the biliary passages. He records his studies on bile sediment after the administration of "decholin" and attaches diagnostic significance to his results. He reviews his results following the use of various therapeutic agents on diseases of the biliary passages, citing numerous cases. Every one interested in the study and diagnosis of disease of the biliary ducts should have a copy of this monograph at hand.

PRACTICAL CLINICAL LABORATORY DIAGNOSIS. By CHARLES C. BASS and FOSTER M. JONES. Third edition. Price, $7.50. Pp. 187. Baltimore: Williams & Wilkins Company, 1929.

The material covered by this book has been chosen rather arbitrarily, as has also been the case in the method selected for each test. For instance, a method is given for determination of blood sugar, but none is included for any determination of blood protein. Only one counting chamber is described and that is not to be found universally. While fourteen pages are devoted to blood counting, no mention is made of the simple theory pertaining thereto. The material which is presented is given clearly although verbosely. Not a few of the many illustrations are valueless though technically good. The book should serve best medical students with a limited premedical and preclinical training.

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